The Pharmacogenomics Journal (2013) 13, 21–26

www.nature.com/tpj

ORIGINAL ARTICLE

Serotonin receptor 2A (HTR2A) gene polymorphism predicts treatment response to venlafaxine XR in generalized anxiety disorder

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Received 2 May 2011; revised 29 July 2011; accepted 8 September 2011; published online 18 October 2011

Generalized anxiety disorder (GAD) is a chronic psychiatric disorder with significant morbidity and mortality. Antidepressant drugs are the preferred choice for treatment; however, treatment response is often variable. Several studies in major depression have implicated a role of the serotonin receptor gene (*HTR2A*) in treatment response to antidepressants. We tested the hypothesis that the genetic polymorphism rs7997012 in the *HTR2A* gene predicts treatment outcome in GAD patients treated with venlafaxine XR. Treatment response was assessed in 156 patients that participated in a 6-month open-label clinical trial of venlafaxine XR for GAD. Primary analysis included Hamilton Anxiety Scale (HAM-A) reduction at 6 months. Secondary outcome measure was the Clinical Global Impression of Improvement (CGI-I) score at 6 months. Genotype and allele frequencies were compared between groups using χ^2 contingency analysis. The frequency of the G-allele differed significantly between responders (70%) and nonresponders (56%) at 6 months ($P=0.05$) using the HAM-A scale as outcome measure. Similarly, using the CGI-I as outcome, the G-allele was significantly associated with improvement ($P=0.01$). Assuming a dominant effect of the G-allele, improvement differed significantly between groups ($P=0.001$, odds ratio $=4.72$). Similar trends were observed for remission although not statistically significant. We show for the first time a pharmacogenetic effect of the HTR2A rs7997012 variant in anxiety disorders, suggesting that pharmacogenetic effects cross diagnostic categories. Our data document that individuals with the HTR2A rs7997012 single nucleotide polymorphism G-allele have better treatment outcome over time. Future studies with larger sample sizes are necessary to further characterize this effect in treatment response to antidepressants in GAD.
The Pharmacogenomics Journal (2013) **13,** 21–26; doi:10.1038/tpj.2011.47; published online 18 October 2011

Keywords: pharmacogenetics; HTR2A; anxiety disorders; treatment response; venlafaxine; rs7997012

Introduction

Generalized anxiety disorder (GAD) is a highly prevalent chronic psychiatric disorder with significant morbidity and mortality. Currently, antidepressant drugs are the preferred choice for acute and chronic treatment; however, treatment response is often variable ranging from 40–70%,[1–3] with some patients responding well to medications while others fail treatment. In general, only a

third of GAD patients achieve remission in the acute phase of treatment,[4,5] and those patients achieving an initial response often suffer relapse.[6,7] The underlying neurobiological mechanisms of treatment response remain unknown, and currently all pharmacotherapy for GAD is essentially determined on a 'trial and error basis'. However, growing evidence suggests that genetic factors influence treatment response and tolerability to medication. The majority of pharmacogenetic studies of antidepressant drugs have been carried out in populations with major depressive disorder (MDD)[8] while only a few reports exist for anxiety disorders.[9]

Recent data indicate a potential role of the gene encoding the serotonin receptor 2A (*HTR2A*) and treatment response to antidepressant drugs in MDD. Several small studies of various antidepressant drugs in various MDD samples have been previously investigated for polymorphisms in the *HTR2A* gene and treatment response and/or adverse events (for review Kato and Serretti[8]). While some studies were positive others could not confirm previous results; however, new interest in the *HTR2A* gene was generated by recent findings of pharmacogenetic studies using the large STAR*D sample.[10] McMahon *et al*.[11] genotyped 68 candidate genes in 1953 patients with MDD from the STAR*D trial who were moderately depressed and treated open-label with citalopram for up to 12 weeks. The main finding was a robust association between the rs7997012 single nucleotide polymorphism (SNP) in the *HTR2A* gene and treatment outcome.[11] Since then, several other groups have independently replicated the finding (Table 1). Peters *et al*. (2009) used the same sample and reconfirmed the association. Lucae *et al*.[12] confirmed an association of the rs7997012 SNP and antidepressant treatment response in two samples of the German origin. Horstmann *et al*.[13] could also replicate the association of the rs7997012 SNP in a sample from Munich, but found stronger support for the HTR2A SNP rs17288723. Uher *et al*.[14] could not confirm the rs7997012 SNP in the genome-based therapeutic drugs for depression sample; however, they found several other SNPs (rs9316233, rs7324218 and rs2224721) in the *HTR2A* gene associated with treatment response to antidepressants. Taken together, several studies document a role of the HTR2A variant rs7997012 and antidepressant treatment response in MDD, with similar effect sizes.

In this study, we addressed the following question: does the HTR2A rs7997012 variant predict antidepressant treatment response in patients with anxiety disorders? We show for the first time a pharmacogenetic effect of the HTR2A rs7997012 variant in GAD, suggesting that pharmacogenetic effects cross diagnostic categories. Our data document that individuals with the HTR2A rs7997012 SNP G-allele have better treatment outcome over time.

Subjects and methods

Patients for this study participated in an 18-month, one-center, relapse prevention study that comprised three treatment phases.[15] A 6-month open-label venlafaxine XR (VEN) flexible-dose treatment phase (75–225 mg per day) (Phase I), a 6-month randomized, double-blind, placebo-controlled relapse phase (Phase II) and a final 6-month randomized, double-blind, placebo-controlled relapse phase (Phase III). Pharmacogenetics analysis was carried out only for patients from Phase I. Detailed methodology of the clinical trial is described elsewhere.[15] Briefly, to be included in the study, subjects had to be 18 years or older and meet the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for GAD as determined by the Structured Clinical Interview and a psychiatric evaluation. Patients had to have sufficient symptoms to require anxiolytic drug therapy, including a score of $\geqslant 20$ on the Hamilton Anxiety Scale (HAM-A) at screen and at baseline, and a score of $\geqslant 4$ on the Clinical Global Impressions-Severity (CGI-S). Patients were also assessed with the 17-item Hamilton Depression Scale (HAM-D). A HAM-D cutoff score of $\leqslant 18$ was used to exclude more seriously depressed patients, and a cutoff score of <2 on the suicide item of the HAM-D was used to exclude suicidal patients. Patient health was determined by physical examination, medical history, and if necessary, laboratory tests and electrocardiogram.

Exclusion criteria were any current anxiety spectrum DSM-IV diagnosis at the threshold but not sub-threshold

Table 1 Positive pharmacogenetic studies of the HTR2A SNP rs7997012

Study	*Phenotype*	N	*Antidepressant treatment*	*Ethnicity*	*Trial length (weeks)*	*Results*	*OR*	*OR dominant model GG+GA vs AA*
McMahon *et al.*[10]	MDD (STAR*D)	1953	Citalopram	Mixed	12	A/A = 18% reduction in risk for being nonresponder	2.26 response	*Unavailable
Peters *et al.*[28]	MDD (STAR*D)	1953	Citalopram	Mixed	12	A-allele associated	1.43 response 1.52 remission	*Unavailable
Lucae *et al.*[12]	MDD (85%) Bipolar (15%)	186	Various	European	6	G-allele associated with better outcome	1.31 remission	5.99 remission
Horstmann *et al.*[13]	MDD	305	Various	European	5	G-allele associated with better outcome	1.57 remission	2.07 remission
Lohoff *et al.*, present study	GAD	112	Venlafaxine XR	European	24	G-allele associated with better outcome	1.50 response 1.88 improvement	3.35 response 4.98 improvement

Abbreviations: GAD, generalized anxiety disorder; MDD, major depressive disorder; OR, odds ratio; SNP, single nucleotide polymorphism.
* Indicates trend since *P* value is slightly above 0.05.

level, current or past history of bipolar disorder, schizophrenia, other psychotic disorders or dementia. An episode of major depression in the previous 6 months or depressive symptomatology at intake (HAM-D > 18), and substance abuse or dependence during the past 6 months were further exclusion criteria. Occasional recreational drug or alcohol use was not an exclusion criterion, thus allowing our sample more closely to represent GAD patients in the community. Urine drug screens for benzodiazepines (BZ), opiates and tetrahydrocannabinol were conducted at regular intervals. Female patients who were pregnant, breast feeding or had a positive urine pregnancy test were excluded. Fertile females had to use an accepted contraceptive method, and urine pregnancy tests were performed at regular intervals. Patients on a low daily dose of BZ anxiolytics or on hypnotics were allowed to enter the trial, and were tapered off their BZ during the first 12 weeks of VEN treatment. Patients were recruited at the University of Pennsylvania Medical Center with approval and oversight by the Institutional Review Board of the University of Pennsylvania. Written informed consent was obtained before performing any study procedures. After the 4–28 days screening period, eligible patients were started on VEN 37.5 mg for 1 week followed by 75 mg per day for the second week. After the second week, flexible dosing was used in a range of 75–225 mg per day. Every attempt was made to raise the patient's daily dose to 225 mg by week 8, unless adverse events prevented this increase or the patient was in remission. After 12 weeks of treatment, patients who were unimproved or worse, having a Clinical Global Impression of Improvement (CGI-I) of $\geqslant 4$, were discontinued from the program as unresponsive. Patients minimally improved (CGI-I score of 3) were continued in the program to assess whether or not longer than 3 months of treatment may produce further clinical improvement.

DNA was obtained, and treatment response was assessed in 156 patients (European–Americans (EA) $n = 112$; African–Americans (AA) $n = 41$; others $n = 3$) that participated in the 6-month open-label phase of venlafaxine XR. Mean age of our population was 49.6 years (range: 18–85 years), and the gender distribution included 64 males and 92 females (males = 41% and females = 59%). Primary analysis included HAM-A reduction at 6 months, response was defined as HAM-A reduction of $\geqslant 50\%$ and remission was defined as HAM-A $\leqslant 7$. Secondary outcome measure was the CGI-I score at 6 months. Improvement was defined as CGI-I of 1 and 2, remission was defined as CGI-I of 1. The last observation carried forward (LOCF) imputation method was used for this study to account for missing data. Due to differences in allele frequencies for the rs7997012 SNP between ethnic groups (EA minor allele frequency: 0.37–0.45; AA minor allele frequency: <0.01), primary analysis was carried out separated by ethnicity. Genotyping of the HTR2A variant rs7997012 was performed using Applied Biosystems (ABI) (Foster City, CA, USA) 'Assays-on-demand' as per manufacturer protocol. Quality control was maintained by genotyping 10% duplicates of subjects. Genotype and allele frequencies were compared between groups using $\times^2$ contingency analysis. A two-tailed type I error rate of 5% was chosen for the analysis.

Results

Genotype distributions were in accordance with Hardy–-Weinberg equilibrium. The concordance rate was 100% with respect to the 10% of samples that were genotyped twice for quality control. Allelic frequencies were consistent with those reported in the HapMap database for Utah residents with Northern and Western Europe ancestry from the CEPH collection. Treatment response to VEN based on genotype for the EA sample using the HAM-A outcome measure over time (last observation carried forward (LOCF)) is shown in Figure 1. Patients with at least one G-allele showed significant reduction in HAM-A score when compared with the A/A group at the main study endpoint of 6 months (A/A group mean HAM-A: 11.38, s.e.: 1.64; G/A + G/G group mean HAM-A: 6.58, s.e.: 0.71; one-way analysis of variance (ANOVA): $F = 7.15$; $P = 0.0086$). Exploratory analysis showed that the difference between groups was statistically significant as early as week 12 (one-way ANOVA: $F = 3.67$; $P = 0.057$), week 16 (one-way ANOVA: $F = 5.44$; $P = 0.021$) and week 20 (one-way ANOVA: $F = 4.48$; $P = 0.036$).

Results for the EA sample ($n = 112$) using a categorical outcome measure of response/improvement and remission are shown in Table 2. We observed a significant association for response (HAM-A) and improvement (CGI-I) after 6 months of treatment. In addition, similar to previously reported findings,[12,13] we show a dominant effect of the G-allele (see also Figure 1). Patients with one or two copies of the rs7997012 G-allele did respond significantly better than patients with an A/A genotype ($P = 0.02$; odds ratio (OR) = 3.35), and showed better improvement at 6 months ($P = 0.002$, OR = 4.98). For the combined sample ($n = 156$), the frequency of the G-allele differed significantly between responders (70%) and nonresponders (56%) at 6 months ($P = 0.05$) using the HAM-A scale as outcome measure. Similarly, using the CGI-I as outcome, the G-allele was significantly associated with improvement ($P = 0.01$). Assuming a dominant effect of the G-allele, and a recessive effect of the A-allele, improvement differed significantly between groups ($P = 0.001$, OR = 4.72). Similar trends were observed for remission in the combined sample although not statistically significant (data not shown).

As the majority of our patients were already participating in various treatment phases of this clinical trial at the time we collected DNA, our sample should be considered nonrandom and overrepresents completers. Completer rates were for the EA sample: baseline: $n = 112$; week 12: $n = 103$; week 24: $n = 89$, which represents an attrition rate of $\sim 21\%$. In comparison, the attrition rate for the first 6 months of our clinical treatment trial was $\sim 42\%$.[15] Exploratory analysis of only EA completers at week 24 ($n = 89$) reveals statistically significant differences between genotype groups (A/A group mean HAM-A: 8.41, s.e.: 1.41; G/A + G/G group mean HAM-A: 4.62, s.e.: 0.55; one-way ANOVA: $F = 6.24$; $P = 0.01$).

Table 2 6-month outcome data: response/improvement (HAM-A) and remission (CGI), European–American sample ($n = 112$)

HTR2A rs7997012	*Sample*	n	*Genotype frequency*			P*	*Allele frequency*	P*	*OR*
			G/G	*G/A*	*A/A*		*f(G)*		
Response HAM-A LOCF	Responders	90	0.36	0.51	0.12	0.060	0.62	0.227	1.50
	Nonresponders	22	0.36	0.31	0.31		0.52		
	G dominant A recessive (G/G+G/A vs A/A)							0.024	3.35
Improvement CGI LOCF	Improvers	91	0.37	0.51	0.11	0.007	0.63	0.063	1.88
	Non-improvers	21	0.33	0.28	0.38		0.47		
	G dominant A recessive (G/G+G/A vs A/A)							0.002	4.98
Remission HAM-A LOCF	Remitters	75	0.38	0.49	0.12	0.24	0.63	0.182	1.46
	Non-remitters	37	0.34	0.43	0.24		0.54		
	G dominant A recessive (G/G+G/A vs A/A)							0.094	2.35
Remission CGI LOCF	Remitters	79	0.127	0.494	0.380	0.314	0.373	0.258	0.71
	Non-remitters	33	0.242	0.424	0.333		0.455		
	G dominant A recessive (G/G+G/A vs A/A)							0.642	0.81

Abbreviations: CGI, Clinical Global Impression; HAM-A, Hamilton Anxiety Scale; LOCF, last observation carried forward; OR, odds ratio.
* Indicates trend since *P* value is slightly above 0.05.

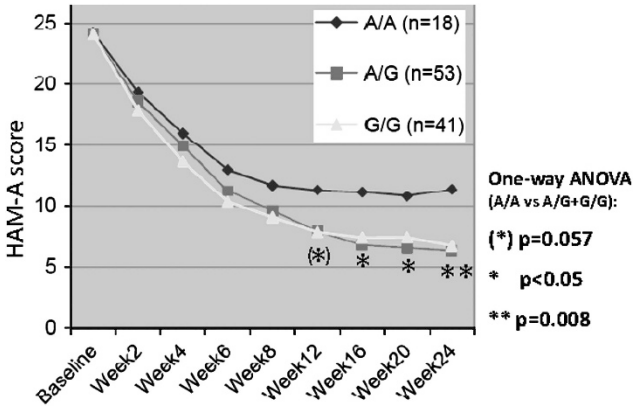

Figure 1 HTR2A rs7997012: treatment response to venlafaxine XR (VEN) (last observation carried forward (LOCF)) based on genotype (European–Americans (EA) sample, $N = 112$).

As the HTR2A rs7997012 variant was initially reported to be involved in treatment response to antidepressant drugs in MDD populations, we conducted secondary analysis using a depression rating scale to evaluate a potential role of this genetic marker on depressive symptomatology in EA GAD patients ($n = 112$). HAM-D scores were available for baseline, week 12 and week 24. There were no statistically significant differences between genotype groups in HAM-D score using LOCF data at baseline or week 12; however, we observed a significant difference in HAM-D score at week 24 between patients with the A/A genotype (mean: 9.33; s.e.: 1.17) and G/A + G/G group (mean: 5.31; s.e.: 0.51; $F = 9.83$; $P = 0.002$).

Discussion

In the present study, we show for the first time a pharmacogenetic effect of the HTR2A rs7997012 variant in anxiety disorders. Our data document that individuals with at least one G-allele have better treatment outcome to VEN over time (Figure 1). Interestingly, this pharmacogenetic effect was increasingly statistically significant as time progressed, with a mean HAM-A difference between the A/A group and the G/A + G/G group of 4.8 at 6 months. Similar to our previous clinical studies that show that GAD patients benefit most from long-term antidepressant treatment,[15] we document here that treatment response in GAD is furthermore influenced by the HTR2A rs7997012 variant. Our results suggest that patients with GAD who have at least one G-allele should continue antidepressant treatment beyond 12 weeks, in order to maximize their potential for response and remission.

Interestingly, several previous studies in MDD have documented a role of the HTR2A rs7997012 variant in treatment response to antidepressants (Table 1). Similar to reports in depression and despite our relatively small sample size, we observed strong effect sizes in particular when considering a dominant model, suggesting that the rs7997012 variant might be a predictor of the general ability to respond to antidepressant therapy regardless of underlying DSM-IV diagnosis. This is further supported by our observation that GAD patients treated with VEN showed also a genotype-dependent improvement in depressive symptomatology at 6 months (A/A: HAM-D = 9.33, G/A + G/G: HAM-D = 5.31; $P = 0.002$). It is still unknown, if the HTR2A variant will also have an effect on non-pharmacological interventions, and future studies will have to incorporate other treatment modalities and preferably a placebo arm.

While no clear data exist on the biological role of the HTR2A rs7997012 SNP, a large body of evidence suggests a role of the HTR2A receptor (HTR2A-R) in mood and anxiety disorders as well as other psychiatric disorders.[16] The HTR2A-R is a G-protein postsynaptic receptor widely expressed in human brain and implicated in prefrontal-subcortical circuits regulating mood/anxiety. Neurobiological data suggest that the HTR2A-R has an important role in antidepressant drug action as several antidepressants downregulate HTR2A-Rs in rodent and primate forebrain correlating with the timeframe of therapeutic onset in

humans.[17–19] Selective HTR2A-R antagonists are effective in animal models of depression, further strengthening the involvement of the HTR2A-R in mood and anxiety disorders.[20–22] Interestingly, a recent report documented that null-mutant mice for the HTR2A-R have reduced inhibition in conflict anxiety, without affecting fear-conditioned or depression-related behaviors.[23] This anxiolytic effect is consistent with the downregulation of HTR2A-Rs under chronic selective serotonin reuptake inhibitor therapy. It is thus feasible to hypothesize that variation in the *HTRA2* gene might contribute to the effectiveness of antidepressants by having functional effects on HTR2A-Rs. To our knowledge, there are no data available documenting an allele-specific effect of rs7997012 on HTR2A signaling *in vitro*. Future studies are needed in this area.

Although our results document a role of the *HTR2A* gene and treatment response to VEN in GAD, there are also several limitations that should be considered carefully. First, it should be noted that patients in this study participated in an 18-month long-term treatment trial of GAD, and DNA samples were collected retrospectively and overrepresent completers, thus there might be an ascertainment bias. Future studies will have to use a prospective clinical trial design to adequately address this concern. Another limitation includes the lack of a placebo arm thus limiting the specificity of HTR2A rs7997012 variant on treatment response to VEN. While it is ethically questionable to withhold FDA-approved treatment from GAD patients for an extended period of time, such as a 6-month double-blind placebo-controlled treatment trial, future studies could include comparison drugs and/or interventions in order to assess the specificity of the rs7997012 variant on treatment outcome. Comorbidity of anxiety disorders and depression is common, and should be considered carefully when interpreting results. Although our sample was a primary GAD sample, with current MDD as exclusion criterion, past episodes of MDD were allowed and patients may have had some moderate depressive symptoms at baseline. Interestingly, our GAD patients improved also on the HAM-D scale depending on the rs7997012 genotype. Future studies with various phenotypic definitions, such as anxious–depression, versus strict GAD might be warranted.

From a genetic perspective, there are several limitations of our study that should be considered. We investigated only one SNP in the *HTR2A* gene, based on the *a priory* hypothesis that this variant, which was previously associated with antidepressant treatment response in MDD, will also have an effect in a sample of GAD patients treated with antidepressant drugs. It is possible that other variants or haplotypes have an effect on treatment response to antidepressant drugs. Future studies will have to comprehensively genotype the *HTR2A* gene region for common and rare variants that might influence HTR2A-R biology and ultimately treatment outcome. The rs7997012 is an intronic SNP, for which no clear biological function has been identified, and might be in linkage disequilibrium with another functional variant in the *HTR2A* gene. This possibility is supported by the observation that both alleles were associated in different directions in various studies. While McMahon *et al* (2006) and Peters *et al* (2009) observed better outcome with the A-allele, Lucae *et al*.[12] and Horstmann *et al*.[13] and our results suggest that the G-allele predicts better outcome. One main difference between these studies was the use of a mixed-ethnicity sample by McMahon *et al* (2006) and Peters *et al* (2009). Another concern of our study is the possibility of a false-positive finding due to population stratification. Although our primary analysis only included individuals of European descent due to the fact that the rs7997012 A-allele is nearly absent in individuals of African descent, undetected differences in population structure might contribute to false-positive results.[24,25] Effective strategies to control for these stratification issues include the use of genomic controls in future studies.[26,27]

In conclusion, we show for the first time a pharmacogenetic effect of the HTR2A rs7997012 variant in anxiety disorders, supporting the hypothesis that variants in the *HTR2A* gene predict treatment outcome to antidepressant drugs, independent of underlying DSM-IV diagnostic category. Our results require careful replication using a prospective clinical trial design to further characterize this effect in treatment response to antidepressants in GAD.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgments

This research was supported by US Public Health Research Grant MH065963 (KR) and K08MH080372 (FWL). The data for this study were collected between 2005 and 2009. We want to thank Wyeth Laboratories for providing all study medication. We also thank Rachel Hodge for technical assistance in genotyping and Dana Patsch for assisting in management and quality assurance for this project. This study was registered under clinical trails.gov.Identifier NCT00183274. KR has received honoraria and served as a consultant or on advisory boards to Cephalon, Eli Lilly, Hoffman-La Roche, Jazz Pharmaceuticals, Johnson & Johnson, Novartis Pharmaceuticals, Pfizer, Epix (PreDix) Pharmaceuticals and PGx Health LLC. KR received research grants (issued to the University of Pennsylvania) from AstraZeneca, Epix Pharmaceuticals, Genaissance Pharmaceuticals (PGxHealth LLC), NIMH, Pamlab, Pfizer and Wyeth Laboratories. All other authors report no financial relationships with commercial interests.

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