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Personality Trait and Antidepressant Type are Potential Moderators of the Association between Genotypes of *HTR1A*-rs6295 or *HTR2A*-rs6311 with Treatment Response

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Abstract

Background: Currently, empiric treatment of Major Depressive Disorder (MDD) relies on the characteristics of the presenting patients.

Aim: The aim of the current study was to identify moderators for the association of SSRI treatment efficacy response phenotype with genotypes of *HTR1A*-rs6295 or *HTR2A*-rs6311 polymorphism in a population of MDD patients.

Materials and methods: The study included 300 patients with MDD. The assessment of Selective Serotonin Reuptake Inhibitors (SSRI) treatment response was based on 50% reduction in the depressive score obtained within 6 weeks of treatment onset on the Montgomery Asberg Depression Rating Scale (MADRS-S) for each patient recruited in the psychiatric clinics of the four tertiary hospitals in the Klang valley region of Malaysia.

Results: The study population was made up of young adults (median age=37.00 years), mostly females (67.1%) with no family history of psychiatric illness (73.4%). MDD patients with the GA genotype for the HTR2A-rs6311 polymorphism and received escitalopram antidepressant were significantly (over-dominant model; P=0.019, OR=0.114 (0.019–0.701)) less likely to respond to treatment. The CG+GG genotype of *HTR1A*-rs6295 gene polymorphism was associated with significantly (recessive model: P=0.019, OR=0.146 (0.026-0.733)) reduced likelihood of responding to antidepressant treatment among the MDD patients with the irritability personality trait.

Conclusion: The association between the CG genotype of the *HTR1A*-rs6295 with poor SSRI treatment response is elaborated among patients that have an irritable personality. The role of medication type in determining the direction of association between genotype of the *HTR2A*-rs6311 with treatment response identified in the literature was also revalidated in the current study.

Keywords: Depression • Moderators • Phenotypes • Pharmacogenetic • Antidepressant

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Introduction

Currently, empiric treatment of Major Depressive Disorder (MDD) relies on the characteristics of the presenting patients. The study included 300 patients with MDD. The assessment of Selective Serotonin Reuptake Inhibitors (SSRI) treatment response was based on 50% reduction in the depressive score obtained within 6 weeks of treatment onset on the Montgomery Asberg Depression Rating Scale (MADRS-S) for each patient recruited in the psychiatric clinics of the four tertiary hospitals in the Klang valley region of Malaysia. MDD patients with the GA genotype for the *HTR2A*-rs6311 polymorphism and received escitalopram antidepressant were significantly (over-dominant model; P=0.019, OR=0.114 (0.019–0.701)) less likely to respond to treatment. The CG+GG genotype of *HTR1A*-rs6295 gene polymorphism was associated with significantly (recessive model: P=0.019, OR=0.146 (0.026-0.733)) reduced likelihood of responding to antidepressant treatment among the MDD patients with the irritability personality trait. Thus, the association between the CG genotype of the *HTR1A*-rs6295 with poor SSRI treatment response is elaborated among patients that have an irritable personality. The role of medication type in determining the direction of association between genotype of the *HTR2A*-rs6311 with treatment response identified in the literature was also revalidated in the current study [1-3].

The lifetime prevalence of MDD is 16.2%. Its associated with high morbidity, attendant loss in productivity and poor quality of life as well as high suicidal tendency and these features are unrivalled by other non-communicable diseases. The absence of universal biomarkers for directing diagnostics and/or treatment options for patient have contributed to the delay in development of more efficient treatment options. In some earlier report, it was reported that lower educational levels, lower family monthly income and a family history of psychiatric illness were socio-demographic characteristics that were more common among MDD patients. It is also well established that there are many biological measures that may play central roles in the development of depression and this may explain the difficulty in identifying biomarkers for determining appropriate treatment options. A vital tool for the clinician that addresses the query as to under what condition does a marker performs optimally is described as a moderator. Thus, it has a prescriptive value. The prescriptive value is in the fact that moderators can suggest the directions for differential treatment (or diagnostic test) selection and planning. Moderators are those variables that have an interactive effect with treatment condition on treatment outcome of interest. It specifically elaborate the sub-population of patients that behave differently for the same outcome under different additional layers of conditions. Some potential moderators that have been reported in the literature fall into one of 6 groups; demographics, severity of illness markers, comorbid disorders, parental psychopathology, psychosocial variables and treatment expectancies. High baseline depression score, low socioeconomic status and presence of other medical or psychiatric conditions have all been postulated to be predictors of treatment response with moderator effect. Personality pathology was common among MDD patients that fail to respond to antidepressant treatment or in some situations they show better response to pharmacotherapy compared to psychotherapy. High HA scores were associated with non-response to AD treatments. High Novelty Seeking (NS) scores were associated with a more poor treatment outcome in many studies. Response to antidepressant treatment had been associated with Self Directedness (SD) personality. There are no studies that evaluated the role played by key socio-demographic, personality and clinical features of MDD patients in the association between genotypes of serotonergic genes with efficacy treatment outcome. The aim of the current study was to determine the predictive role of *HT2A*-rs6313 and *HTR1A*-rs6295 gene polymorphism in antidepressant treatment outcome in line with some moderating factors of sociodemographic and personality features [4-7].

Materials and Methods

This study is the pharmacogentic wing of a larger case-control (300 cases: 300 controls) MDD study. The detailed methodology of both the diagnosis and pharmacogenetic wings of the MDD studies had been described in earlier publication. In the earlier pharmacogenetic study, only 142 cases of MDD patients were assessed for association between the *HTR2A*-rs6311 and *HTR1A*-rs6295 polymorphisms with SSRI treatment outcome.

The current study included an additional 158 participants to make up the 300 patients with MDD undergoing SSRI treatment for 6 weeks assessed. As previously described, the MDD patients recruited were 18-65 years of age, diagnosed with first episode of MDD, placed on treatment with SSRI for atleast 6 weeks with verifiable means (records or direct interview) of determining treatment response within this time. The assessment of SSRI treatment response was based on reduction in the depressive score obtained within 6 weeks of treatment onset on the Montgomery Asberg Depression Rating Scale (MADRS-S) for each patient recruited in the psychiatric clinics of the four tertiary hospitals in the Klang valley region of Malaysia. Any patient with a 50% decrease in MADRS score within the 6 weeks period was designated as a treatment responder, while those with less than 50% decrease in MADRS score were described as treatment non-responders [8-11].

Detailed information regarding personality types and traits were obtained from each patient using the temperament and personality questionnaire. Socio-demographic as well as clinical features were also measured for each of the study participants. Bivarate analysis between the socio-demographic/personality features and treatment outcome as well as between genotypes from *HTR2A*-rs6311 or *HTR1A*-rs6295 with treatment outcome, based on a paired classification of each of the socio-demographic/personality features, was done. The adjusted statistical evaluation of the later analysis was also done, using the gender, ethnicity and age [12,13].

Statistical assessment were calculated using *chi-square* and logistic regression. The alpha value (p value) were adjusted for multiple testing by dividing the alpha value by the number of bivariate assessment done for each output. Specifically, the alpha value adopted for the Association between treatment response after 6 weeks treatment with Selective Serotonin Reuptake Inhibitors (SSRI) and socio-demographic/clinical features was $p \leq 0.0055$ (0.05/9). The P value adopted for the assessment of the association between treatment response and socio-demographic/clinical features was $p \leq 0.005$ (0.05/10). The p value adopted for the assessment for the crude and adjusted evaluations for the moderating effect of some socio-demographic and clinical features of MDD patients in the association between treatment outcome and genotypes of HTR1A-rs6295 or HTR2A-rs6311 was $p \leq 0.01$ (0.05/5) [14].

Results

The socio-demographic as well as clinical features of the study participants were measured appropriately and reported in Table 1.

The study population was made up of young adults (median age=37.00), mostly females (67.1%) of low socio-economic status (70.6%) who profess to the Islamic faith. Most of the participants have been in some form of marriage or relationship (52.8%) and they had no family history of psychiatric illness (73.4%). The various categories of "temperament and personalities" identified among the study participants included anxious worrying (73.4%), reserve (81.5%), perfectionism (97.2%), irritability (84.8%), social avoidance (89.9%), interpersonal sensitivity (69.1%), self-focused (80.7%), cooperativeness (56.3%) and effectiveness (66.9%) (Table 1).

Character	Labelling	Frequency/Value	Percentage
Age	Median-age (minimum-maximum)	37.00 (18-65)	
Gender	Male (n)/females (n)	94/192	32.9%/67.1%
Medication	Escitalopram/other SSRI	62/224	78.3%/21.7%
Family income	Low/High	202/84	70.6%/29.4%
Work status	Employed/Students/Others	155/40/91	52.8%/14.0%/31.8%
Marital status	Single/Married and others	113/173	39.5%/60.5%
Education	Basic/Advanced	127/159	44.4/55.6
Religion	Islam/Buddhist/Hindu/Christianity/Others	148/64/44/25/5	51.7/22.4/15.4/8.7/1.7(%)
Family history of psychiatric	Yes/No	76/210	26.6/73.4
Chronic disease	Yes/No	102/184	35.7%/64.3%
Anxious worrying	Yes/No	210/69	73.4%/24.1%
Reserve	Yes/No	221/50	81.5%/18.5%
Perfectionism	Yes/No	278/8	97.2%/2.8%
Irritability	Yes/No	235/42	84.8%/15.2%
Social avoidance	Yes/No	249/28	89.9%/10.1%
Interpersonal sensitivity	Yes/No	188/84	69.1%/30.9%
Self-criticism	Yes/No	80/196	29.0%/71.0%
Self-focused	Yes/No	222/53	80.7%/19.3%
Cooperativeness	Yes/No	152/118	56.3%/43.7%
Effectiveness	Yes/No	176/87	66.9%/33.1%
Duration of depression	6 (1-96) months		
Baseline MADRS score	26 (1-60)		
HTR1A-rs6295 genotypes	CC/CG/GG	135/103/48	47.2%/36.0%/16.8%

HTR2A-rs6311 genotypes	GG/GA/AA	65/115/106	22.7%/40.2%/37.1%

Table 1. Socio-demographic and clinical features in the study population.

The association of the various socio-demographic features with the phenotype of treatment response was also evaluated in the current study and presented in Table 2.

The proportion of responders was more than the non-responders to SSRI treatment. The common socio-demographic features of the patients included; more females, no chronic disease, SSRI type-on luvox (and other SSRIs) and low family income, employed, once married (including previously married), low educational level and no family history of psychiatric illness. It was also observed that most of the study participants were responders to SSRI treatment and their common socio-demographic features were in keeping with the commonest socio-demographic features of the combined study population earlier described. Nevertheless, none of the association between the socio-demographic features and treatment response phenotype was statistically significant in the current study (Table 2) [15,16].

		Responder	Non-responder	
Chronic disease	Yes	75	27	X^2=0.375, df=1, P=0.540
	No	129	55	
Ethnicity	Malay	96	46	X^2=1.920, df=2, P=0.383
	Chinese	67	22	
	Indian	41	14	
Gender	Male	64	30	X^2=0.720, df=1, P=0.396
	Female	140	52	
Medication	Luvox and other	162	62	X^2=0.498, df=1, P=0.480
	Escitalopram	42	20	
Family income	Low income	141	63	X^2=0.784, df=1, P=0.376
	High income	61	21	
Jobs status	Employed	108	47	X^2=0.755, df=2, P=0.686
	Student	28	12	
	Others	68	23	
Marital status	Single	76	37	X^2=1.515, df=1, P=0.218
	Married (including previously married)	128	45	
Family history of psychiatric illness	Yes	52	24	X^2=0.428, df=1, P=0.513
	No	152	58	
Educational level	Low	118	41	X^2=1.457, df=1, P=0.227
	High	86	41	

Table 2. Association between treatment response after 6 weeks treatment with Selective Serotonin Reuptake Inhibitors (SSRI) and socio-demographic/clinical features.

The association of the different phenotypes of personality types and traits were also evaluated for association with treatment response phenotype in the current study (Table 3) [17].

		Non-responder	Responder		
Anxious-worrying	No	157	53	X^2=5.93, df=1, OR=2.023 (1.14-3.59)	P=0.015,
	Yes	41	28		

Personal-reserve	No	158	63	X^2=0.24, df=1, P=0.624
	Yes	34	16	
Perfectionism	No	198 (71%)	80 (29%)	Not computed
	Yes	0	0	
Irritability	No	170	65	X^2=1.88, df =1, P=0.171
	Yes	26	16	
Social-avoidance	No	180	69	X^2=1.64, df=1, P=0.200
	Yes	17	11	
Interpersonal sensitivity	No	143	45	X^2=8.79, df=1, P=0.003, OR=2.27 (1.31-3.93)
	Yes	49	35	
Self-criticism	No	67	13	X^2=9.32, df=1, P=0.002; OR=2.74 (1.41-5.31)
	Yes	128	68	
Cooperativeness	No	102	50	X^2=2.72, df=1, P=0.099
	Yes	90	28	
Self-focused	No	161	61	X^2=0.879, df=1, P=0.349
	Yes	35	18	
Effectiveness	No	120	56	X^2=2.84, df=1, P=0.092
	Yes	68	19	

Table 3. Association between treatment response and socio-demographic/clinical features.

The association between personality trait of anxious-worrying (X^2=5.93, df=1, P=0.015, OR=2.023 (1.14-3.59)), self-criticism (X^2=9.32, df=1, P=0.002; OR=2.74 (1.41-5.31)) and interpersonal sensitivity (X^2=8.79, df=1, P=0.003, OR=2.27 (1.31-3.93)) with treatment response were statistically significant (Table 3). Self-criticism was associated with better response to treatment when compared to those patients without the self-criticism personality. Patients with the anxious-worrying personality are more likely to respond to treatment compared to those without the personality type. Relatively, when compared with those patients without the interpersonal-sensitivity for both response and non-response to treatment, the patients with the interpersonal-sensitivity were more likely to respond to treatment [18,19].

Marital status and the status of family income have an interactive effect with the phenotype of treatment efficacy response when evaluating its association with genotype of *HTR1A*-rs6295 polymorphism. Single (unmarried) participants with the GG genotype of the *HTR1A*-rs6295 polymorphism were significantly (homozygote model (P=0.046, OR=0.194 (0.039-0.969); Dominant model (P=0.057, OR=0.220 (0.046-1.045)) less likely to report a clinical treatment.

MDD patients who had the GG+AA genotype for the *HTR2A*-rs6311 polymorphism and received escitalopram anti-depressant were significantly (over-dominant model (crude statistics: P=0.013, OR=0.135 (0.028–0.654); adjusted statistics: P=0.019, OR=0.114 (0.019-0.701)) less likely to respond to treatment when compared to those with the AA genotype. The CG+GG genotype (recessive model) of *HTR1A*-rs6295 gene polymorphism was associated with significantly (recessive model (crude statistics: P=0.044, OR=0.244 (0.062-0.965)); Adjusted statistics: P=0.019, OR=0.146 (0.026-0.733)) reduced likelihood of responding to antidepressant treatment among the MDD patients with the irritability personality trait. A similar significant association was observed for CG genotype (heterozygous model (Adjusted statistics: P=0.026, OR=0.157 (0.031-0.798))) and over-dominant model (Adjusted statistics: P=0.033, OR=0.173 (0.035-0.868)) of *HTR1A*-rs6295 gene polymorphism with reduced likelihood of treatment response in irritable MDD patients [20].

Discussion

The patients in this study were largely young, employed, females, of low socioeconomic status, married (including previously married (widowed, separated and divorced)), well-educated with no family history of psychiatric illness. Although, the proportion of responders is higher than the proportion of non-responder, distribution of the socio-demographic features based on treatment outcome was similar to that of the combined study population described earlier. None of the socio-demographic features evaluated in the current study was statistically significantly associated with SSRI treatment outcome. However, the anxious-worrying, self-criticism and interpersonal sensitivity personality traits were associated with SSRI treatment response

among the MDD patients. In the pharmacogenetic arm of the current study, patients who were single and had an irritable personality type were more likely to have a poor response to SSRI treatment when they have the GG genotype (or carry the G-allele) of *HTR1A*-rs6295 polymorphism. When all MDD patients who have homozygous genotype (the GG+AA genotype) for the *HTR2A*-rs6311 polymorphism were combined together and compared to those with the heterozygote genotype (GA of *HTR2A*-rs6311), the patients with the later genotype were significantly less likely to respond to treatment with escitalopram. The association between the genotypes of the *HTR2A*-rs6311 polymorphism with treatment outcome was not observed among patients treated with other SSRI medication. Although adjustment of the alpha value for multiple testing did not support the association result, nevertheless, the potential for association remains plausible in such scenario when more samples are recruited into the study.

The socio-demographic features of age and gender for the study participants in this study was similar to those in earlier studies that evaluated the role of socio-demographic and clinical features in relations to MDD treatment outcome. The literature were awash with reports for association between high Harm Avoidance (HA), high Novelty Seeking (NS) and low self-directedness scores with non-response to AD treatments. Personality features appear to consistently play a role in treatment outcome. The personality features identified to be associated with the SSRI treatment response in this study (anxious worrying, self-criticism and interpersonal sensitivity) were very different from the personality features highlighted in the literature. The reason for the disparity in the specific personality feature highlighted in the earlier study and the current one, may stem from the differences in the study design in terms of study participants evaluated (treatment resistant MDD *vs.* unipolar MDD only), medication (Paroxetine or other SSRI) used for treatment, definition of the treatment response phenotype as well as the study sample size and recruitment criteria.

In the literature, the role of maladaptive responses to negative feelings in the aetiology and persistence of depressive episodes have been reported. The earliest symptom of depression that was commonly attenuated during SSRI treatment was 'biased emotional information processing towards negative emotions' and other appreciable clinical improvement takes place weeks after commencement of treatment. Self-criticism has been defined as a response pattern to perceived failure and it is characterized by self-judgment and self-evaluation that are entirely negative. The higher the level of negative emotions directed at oneself (very self-critical) with associated irritability and poor capacity to cope with these emotions the higher the risk for individuals to develop a depressive episode that can become persistent. High grade of self-criticism appears to be remedied through some key therapeutic focus including inter-personal relationship, perfectionism as well as issues of self-esteem. The irritability feature is well known to affect the capacity for self-regulation with associated higher level of depression and thus remains a predictor of depression in later life. The association between irritability and depression appears to have a shared genetic risk as demonstrated in earlier studies among different population (Sweden, United Kingdom and United States of America) of adolescent twins followed prospectively. The relationship between depression and irritability extends to the similarity in the types of medication, Serotonin Reuptake Inhibitor (SRI), atomoxetine and norepinephrine, which are effective in treating both conditions. Ameliorating the irritability features can also play a key role in attenuating the risk of developing depression and also the risk for its persistence.

There are numerous studies that evaluated the role of anxious-depression (depression with high level of anxiety symptoms) in predicting antidepressant treatment outcome. Presence of the anxious-depression trait was associated with poor antidepressant treatment efficacy response.

A role of personality features of irritability was observed to moderate the association of the genotype of *HTR1A*-rs6295 gene polymorphism with treatment efficacy outcome. The consistency in the allele/genotype implicated in poor treatment response for the different hereditary models (recessive, homozygous and over-dominant) of the *HTR1A*-rs6295 gene polymorphism among patients with the irritability features was also a pointer at the veracity of the association. This finding elaborates the earlier underlying relationship shared between depression and irritability as well as increase the usefulness of that information for the goal for personalized medicine. Thus, narrowing the poor response phenotypes to irritable MDD patients with the GG genotype (or carry the G-allele) of *HTR1A*-rs6295 polymorphism. It also lends credence to the fact that depression is a complex of syndromes that may need to be unbundled into its components for optimum identification of endophenotypic markers.

In the literature, there are numerous studies that reported higher incidence of mental disorder such as depression among previously married (divorced/widowed) individuals and it was usually attributed to social isolation and stigma that precedes marital distress. Similarly, some earlier studies reported that the incidence of depression among married women was also higher when compared to the married men. And this had been attributed to issues such as migration to husbands place after marriage, marital separation due to transfer of husband and pregnancy. Other factors reported included; miscarriage/abortion, disturbance of sexual cycle attributable to dysmenorrhea/menopause and weight gain/loss. Thus, single (un-married) status or married status (including previously married) can both be implicated in the development of depression. In the current study, the finding that single un-married patients carrying the GG genotype of *HTR1A*-rs6295 were more likely to report failure to respond to treatment was very novel. Although, there are association studies between treatment outcome and marital status, there were no literature report on the role of marital status in moderating the association between genotype of *HTR1A*-rs6295 with treatment efficacy response. Thus, there is need for replication of this findings in future studies.

There are pharmacogenetic studies that had revealed an association between antidepressant treatment response for MDD patients with *HTR2A*-rs6311 and other HTR2A gene polymorphisms such as; *rs7997012*, *rs6313*, *rs1928040*, *rs6308*, *rs6304* and *rs677702*. Specifically, in a cohort of Caucasian patients, the heterozygous (C/T) genotype for *HTR2A*-rs6314 polymorphism was associated with improved health following treatment with antidepressant. In another study in a mixed population of Caucasians and a few African-Americans, the A-allele of *HTR2A*-rs7997012 was associated with an 18% increase in absolute risk for antidepressant treatment response. In a study populated with Japanese MDD patients receiving fluvoxamine treatment for 6 weeks, the assessment for association between the genotypes of *HTR2A*-rs6311 with treatment response was not statistical significant. And this was not similar to the result of another study among Japanese patients treated with fluvoxamine for 6 weeks in which, the 1438G/G genotype of *HTR2A* was associated with a good response to fluvoxamine (SSRIs). The probable reason for the difference in association finding was probably because the latter study recruited patients with recurrent MDD while the former study involved a population of unipolar MDD patients. This literature reports suggest that the underlying association between genotypes of *HTR2A*-rs6311 with fluvoxamine treatment response depends on the phenotype of MDD evaluated. The current study observed an association between GA genotypes of *HTR2A*-rs6311 with poor treatment response among patients treated with escitalopram only (the association was not significant among patients treated with other SSRIs). This was in keeping with the earlier reports that suggested that fluvoxamine was only effective in phenotypes of MDD other than the unipolar variant, which was the population of study participants in the current study. It is important to note that the comparator study from the literature involved only the completed data from 54 unipolar MDD patients receiving treatment with fluvoxamine for 6 weeks while the fluvoxamine (with few on sertraline) study wing in the current study involved 143 or 224 study participants on SSRI (mainly fluvoxamine) for 6 weeks. Thus, suggesting that a similar association result may be obtained even with higher sample size of well-defined phenotypes of MDD treatment outcome with genotypes of *HTR2A*-rs6311 polymorphism. The basis for the current association finding may involve a number of features especially related to the activity of the alleles. Specifically, the mutant allele for *HTR2A*-rs6311 was characterized with increased expression of the encoded receptors and the wild variant was associated with low expression. Low expression of the HTR2A-rs6311 gene predispose patients to high levels of SSRI activities. Thus, from the current results, it appears that the heterozygote genotype may be the worst genotype for the optimal activity of the escitalopram antidepressant medication in treating unipolar MDD. Another feature that may underlie the current association finding may be related to the strong presence of the irritability personality feature in the unipolar MDD patients. The presence of the irritability feature adds an additional layer of burden to the clinical set up of the patients, thus, phenotypically tilting the clinical scenario to a moderate-severe status for the unipolar depression, which is poorly managed with escitalopram among patients with the GA genotype of *HTR2A*-rs6311 polymorphism.

Conclusion

The association between the CG genotype of the *HTR1A*-rs6295 gene polymorphism with poor SSRI treatment response is assuredly elaborated among patients that have an irritable personality type. A role of marital status in moderating the association between genotype of *HTR1A*-rs6295 with treatment efficacy response was identified. There was a role of treatment type (escitalopram) in the association between GA-*HTR2A*-rs6311 genotype with treatment response. Although the different associations identified did not survive the Bonferonni corrections, nevertheless, the current study identified the potential for replicating an association in a larger study.

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Conflict of Interest

The authors declare no competing interests.

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