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# Association study of two *serotonin 1A receptor* gene polymorphisms and fluoxetine treatment response in Chinese major depressive disorders

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**Abstract** The firing rate of dorsal raphe serotonergic neurons is modulated by somatodendritic 5-hydroxytryptamine 1A (HTR1A) autoreceptors. Evidence from animal and clinical studies has suggested that desensitization of HTR1A is implicated in the antidepressant therapeutic mechanism of selective serotonin reuptake inhibitors (SSRIs). Recent studies, including our recent findings, have reported that a functional *HTR1A* C-1019G polymorphism in the promoter region, as well as a nonsynonymous polymorphism, Gly272Asp, may be associated with SSRI pharmacogenetics. In this study, we tested whether Gly272Asp genetic variants are related to a 4-week fluoxetine antidepressant effect in 222 Chinese major depressive patients. We also tested the linkage disequilibrium (LD) measurement between *HTR1A* Gly272Asp and C-1019G polymorphisms, and haplotype analysis was conducted to assess the association between the two markers within the *HTR1A* gene and fluoxetine antidepressant response. The results show that the *HTR1A* Gly272Asp polymorphism was not associated with fluoxetine therapeutic response. The two markers are in strong LD and the *HTR1A* haplotype of the two polymorphisms is associated with fluoxetine therapeutic response. This association is gender-specific and mostly arises from the effect of *HTR1A* C-1019G polymorphism: female patients with -1019C/C genotype showed a better response than -1019G carriers. These findings need to be confirmed in other ethnic populations.


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## 1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) are currently the first-line agents for treatment of major depression. The mechanisms underlying the antidepressant effects of SSRIs are still unclear. Although all SSRIs share almost no molecular feature, one common feature of SSRIs is that they have specific activity in the inhibition of serotonin reuptake, which leads to a tonic elevation of serotonin levels (Nutt et al., 1999). Since SSRIs induce increased serotonin levels in the extracellular space, their therapeutic effect is probably medicated, at least in part, by action at various serotonin receptors. Currently, at least 14 mammalian serotonin receptor subtypes, differing in structure and distribution, have been identified. Among them, serotonin 1A receptor (HTR1A) is expressed as a postsynaptic receptor as well as the major somatodendritic autoreceptor on serotonergic raphe neurons (Sotelo et al., 1990). Data from both animal and human studies have suggested that SSRI therapeutic effects seem to be related to desensitization of somatodendritic HTR1A in the raphe nuclei, which is induced by the increase in serotonin concentration in the extracellular space (for review, see Newman et al., 1993; Stahl, 1998). This notion is further supported by the finding that there is a significant augmenting effect when the beta-adrenergic/HTR1A receptor antagonist, pindolol, was coadministered with SSRI treatment (Bordet et al., 1998).

Pharmacogenetics investigate individual possible genetic factors involved in response to clinical drug treatment, including those factors related to drug metabolism and those related to drug targeting. Since HTR1A has been implicated in the SSRI therapeutic mechanisms, genetic variants in the *HTR1A* could be candidates for SSRI pharmacogenetic study. The *HTR1A* gene, mapped to chromosome 15q11, is intronless and codes a 422-amino-acid protein (Kobilka et al., 1987). Recently, our team and another two research teams have reported a common promoter polymorphism (C-1019G; rs6295 (http://www.ncbi.nlm.nih.gov/SNP/snp_ref.cgi?rs=6295)) of *HTR1A* as being associated with SSRI treatment efficacy in bipolar or unipolar depression (Serretti et al., 2004; Lemonde et al., 2004; Hong et al., 2006). It is possible that this polymorphism may directly affect the SSRI effect on desensitization of the somatodendritic HTR1A receptor or the association of this *HTR1* polymorphism and SSRI antidepressant response is due to linkage disequilibrium (LD) between this polymorphism and a nearby functional polymorphism (Hong et al., 2006). Recently, study of Japanese patients found that a nonsynonymous *HTR1A* polymorphism (Gly272Asp) was associated with fluvoxamine (an SSRI) antidepressant response (Suzuki et al., 2004). This result prompted us to study whether or not this Gly272Asp polymorphism may play a role in SSRI pharmacogenetics in the Chinese population. In addition, LD measurement between *HTR1A* Gly272Asp and C-1019G polymorphisms and haplotype analysis were conducted to assess the association between the two markers within the *HTR1A* gene and SSRI antidepressant response.

## 2. Methods and patients

This is an extended study of our previous report (Hong et al., 2006). The study population consisted of 222 patients with major depression (male/female: 94:128; mean age: 44.0 years [SD: 16.3]) who met DSM-IV criteria and completed a 4-week therapeutic evaluation of fluoxetine. A senior psychiatrist (YWY) made the diagnosis by interviewing patients and family members and also by obtaining records whenever possible. Other inclusion criteria were a minimum baseline score of 18 on the 21-item Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1967) and presence of depressive symptoms for at least 2 weeks before entry into the study without antidepressant treatment during that period (patients were fresh cases or had quit antidepressants for more than 2 weeks). Exclusion criteria were additional current DSM-IV Axis I diagnoses (including substance abuse, generalized anxiety disorders, panic disorders, or obsessive compulsive disorders), personality disorders, pregnancy, recent suicide attempt, and major medical and/or neurological disorders. The entire sample consisted of Taiwanese ethnic Han Chinese. The study was approved by the Ethnics Committee of the Taipei Veterans General Hospital and the study was carried out in accordance with the principles of the Declaration of Helsinki. Written, informed consents were obtained from all subjects.

For the fluoxetine treatment, the daily doses were 20 mg/day in the beginning, and based on the clinical response after 2 weeks of treatment, the investigator could increase the dosage to 40 mg/day. Treatment efficacy was evaluated by one investigator (YWY), blind to patient genotype, who administered the HAM-D Scale before and after the 4-week fluoxetine treatment. Responders were defined as patients with at least a 50% decrease in HAM-D total score after 4 weeks of fluoxetine treatment.

For *HTR1A C-1019G* genotyping, genomic DNA was extracted from EDTA-anticoagulated venous blood samples. The genotyping method was listed in our previous report (Hong et al., 2006). Genotyping for *HTR1A Gly272Asp* polymorphism was done according to a previous report (Suzuki et al., 2004). Polymerase chain reaction (PCR) amplification was performed with the following primers: 5′ CCG CAA GAC GGT CAA AAA GG 3′ and 5′ AAG GTG CCC ATG ATG CC 3′. A final PCR product of 384 base pairs (bp) was obtained. PCR products were digested using *Fok*I restriction enzyme, and the digested fragments were separated on 4% agarose gels. The restriction pattern was *Gly*: 384 bp; *Asp*: 232 and 152 bp.

Comparisons of genotype frequencies between responders and non-responders were done for each polymorphism using chi-square or Fisher's tests. The probability of a type one error was set at a maximum level of 0.05. Data are presented as the mean (standard deviation, SD).

The software SNP Alyze® V3.2 program (Dynacom Co., Ltd., Kanagawa, Japan) was used to evaluate the status of pairwise LD for the two studied polymorphisms to infer the haplotype frequency and to examine the difference of haplotype frequency between groups. The significance level of these analyses obtained from the SNP Alyze® V3.2 was set as $P$ value $<0.05$ after 100,000 permutation tests.

## 3. Results

The mean fluoxetine doses for the 222 patients was 26.0 mg/day [SD: 9.4] at week 4 and 83 (37.3%) of the 222 patients had at least a 50% decrease in HAM-D total score after 4 weeks of taking medication. There were no significant differences in gender or baseline HAM-D score between the responder and the non-responder groups (Table 1); however, the non-responder group had an older mean age compared with the responder group ($P=0.047$).

Genotype distributions for all of the two genetic polymorphisms tested were in Hardy-Weinberg equilibrium. For the *HTR1A* Gly272Asp polymorphism, no 272Asp