LETTER TO THE EDITOR
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Serotonin Receptor 2C -759C/T Polymorphism and Weight Change or Treatment Response to Mirtazapine in Korean Depressive Patients

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Dear Sir.

I have read with great interest the paper by Dr. Lee and colleagues that investigated whether or not the serotonin receptor gene polymorphism (5-HT2C -759C/T) may be associated with a response to mirtazapine or mirtazapine-induced weight gain in patients with major depressive disorder (MDD) in Korean population.[1] They reported that weight change and treatment response after mirtazapine administration was not significantly different among the three 5-HT 2C -759 C/T genotypes. The authors concluded that the 5-HT 2C receptor -759C/T polymorphism may not be associated with treatment response and weight change after 8 weeks of mirtazapine treatment.

To my knowledge, their study is the first one directly investigating the association of 5-HT2C -759C/T with treatment response and weigh change to mirtazapine in Asian patients with MDD, although it failed to demonstrate any valuable pharmacogenetic findings. Hence various comments and standpoint from other researcher will add up more information for future studies.

The acceptable scientific backgrounds for their study may come from several viewpoints: firstly, the 5-HT 2C receptor has different transcriptional activity according to the 5-HT2C -759C/T polymorphism (rs3813929)[2]; secondly, Abnormalities of the 5-HT2C receptor activity have been suggested to be involved in susceptibility and treatment response in MDD.[3] Despite the clear role of 5-HT2C receptor in antidepressant effects has not been fully explained, the 5-HT2C receptor has been found to be directly implicated in the action mechanism of numerous antidepressants.[3] In addition, paroxetine treatment has been proposed to be implicated in functional desensitization of the 5-HT2C receptors.[3]; thirdly, a number of studies have suggested potential association of -759C/T polymorphism with the susceptibility to weight gain after various psychotropic agents,[4] although currently available data still indicates that the exact role of it with weight gain should be more explored in a larger studies.[5,6] Finally, mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA). The enhancement of serotonergic neurotransmission of mirtazpine is specifically mediated by stimulation of 5-HT1 receptors, while mirtazapine antagonizes postsynaptic 5-HT2 receptor.[7] Regarding direct antagonistic activity of mirtazapine on 5-HT2 receptor, it may result in a stimulation of dopaminergic and adrenergic pathways, implementing antidepressant action in behavioral paradigms as well as favoring sleep and sexual function.[8]

Despite aforementioned backgrounds, Dr Lee and colleagues failed to find any association of the -759C/T polymorphism and treatment response/weight change after treatment with mirtazapine, we have to look inside of their study to improve our future researches. The most important issue of the study is an absolute small number of sample included in the study. According to the study results, they continuously present confusing results by a gender without any consistency in results format. However, when we only consider 243 female patients for sample size calculation on treatment response by 3 genotypes, In addition, a set of $p \leq 0.05$ as statistical significance was not properly set since they have tried to test a numerous clinical variables and hypothesis, all p-values should be at least set at approximately 0.0035 level (baseline parameters, responder analysis, HAMD time variation, HAMD sub-

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group analysis and weight changes). Assuming these parameters, the sample power set at 80% and $p \leq 0.01$ level should be at least 354 for female patients when looking at those carrying the CC genotype as compared with those carrying the CT genotype in HAMD difference (given that difference=2.25 and standard deviation=5). Hence the sample size was definitely insufficient for the study. In particular, the TT genotype carriers were only 4 in female (CC=183 and CT=56), clearly indicating a deviation of genotype pooling that is very likely to give negative results on such primary endpoints. Regarding weight changes, the authors may have better chance to have positive results if they have reanalyzed the data T or C carriers (especially criteria of >7% weight gain) rather than each genotype considering absolute less number of TT genotype. Some positive results by such grouping analysis were in fact demonstrated in other similar studies. For example, in another Korean data, T carriers were found to be less likely to have substantial weight gain (>5%) and such association was supported by the repeated measures analysis even after controlling for possible confounding effects, although the whole sample size was only 84 (female=39).[9]

Finally 5-HT2C -759C/T is likely in linkage disequilibrium with other functionally relevant variants that are more directly implicated in the pathogenesis of MDD. Future studies including re-sequencing of 5-HT2C -759C/T or epistatic interaction of 5-HT2C -759C/T with adjacent functional polymorphisms are warranted to identify such variants and to determine how they may contribute to the therapeutic and side effect mechanism of antidepressant.

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