Dopamine (DRD 2) and Serotonin (HTR 2A, 2C) Receptor Gene Polymorphisms do not influence early response to Risperidone in South Indian Patients with Schizophrenia

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Dopamine (*DRD2*) and Serotonin (*HTR2A, 2C)* Receptor Gene Polymorphisms do not influence early response to Risperidone in South Indian Patients with Schizophrenia

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ABSTRACT

Treatment response to antipsychotic drugs is variable and conflicting results have been obtained while studying the influence of *DRD2* and *HTR2* genetic variants on antipsychotic drug efficacy. To explore further, the present study aimed to assess the influence of *DRD2* -141 C Ins/Del, Taq1A and *HTR2A* -1438 G/A, 102T/C and *HTR2C* -759 C/T genetic polymorphisms in response to risperidone in patients with schizophrenia. The study was conducted among the n=320 South Indian patients with schizophrenia who received risperidone treatment (4-8 mg per day) for a minimum of four weeks. Genotyping was done by real-time PCR. Antipsychotic response was assessed using CGI-I score in cross-sectional group, PANSS score in prospective group at baseline and after receiving the risperidone therapy. *DRD2* -141 C Ins/Del (n=310, Ins/Ins=177, Ins/Del+ Del/Del=133, OR 0.70, 95% CI 0.4-1.2 *p* 0.2), Taq1A (n=320, AA=35, AG=132, GG=153, *p* 0.2), *HTR2A* -1438 G/A (n=320, AA=39, AG=164, GG=117, *p* 0.2), *HTR2A* 102T/C (n=320, CC=115, CT=165, TT=40, *p* 0.1) *HTR2C* -759 C/T (females n=132, CC=65, CT+TT=67, OR 1.3, 95% CI 0.6-2.8, *p* 0.5; males n=186, C=120, T=66, OR 1.2, 95% CI 0.6-2.4, *p* 0.4) genetic polymorphisms did not show any association with antipsychotic response to risperidone. *DRD2* -141 C Ins/Del, Taq1A, *HTR2A* -1438 G/A, 102T/C and *HTR2C* -759 C/T genetic variants are not associated with antipsychotic response to risperidone.

Key words: Risperidone, Schizophrenia, Dopamine, Serotonin, Genetic Polymorphism

INTRODUCTION

Schizophrenia (SCZ) a severe psychotic illness requires long term therapy with antipsychotics. Atypical antipsychotics (AAP) act by binding to dopamine (DRD2) and serotonin (5HT) receptors [1]. Clinical efficacy of AAP is highly correlated with potent binding affinity to DRD2 and 5HT receptors [2]. However, a high level of response variability to antipsychotic treatment has been described with regard to acute response, relapse prevention, and side effects. In particular, for the treatment of an acute phase, it is estimated that at least 30 - 40% of the patients do not respond to the treatment [3,4]. There are no biological markers available to predict therapeutic response and tolerance, thereby leading to lengthy empirical trials with an uncertain outcome. Genetic variation may play a role in AAP response variability and several lines of evidence suggest that polymorphisms within genes coding for proteins implicated in the dopamine and serotonin neurotransmission may influence the AAP efficacy in SCZ [5,6]. In this context, several pharmacogenetic studies have been performed to investigate the implication of dopaminergic and serotonergic candidate genes in AAP response [7]. In particular, polymorphisms in *DRD2*, *HTR2A* and to a lesser extent in *HTR2C* genes have been extensively studied in relation with AAP response in SCZ [8,9]. Several studies have shown that the -141C Ins/Del and the Taq1A polymorphisms of the *DRD2* gene may be associated with a reduced receptor density which may alter the therapeutic response [10,11]. Previous study reports showed that Ins allele carriers of -141C Ins/Del polymorphism and A1 allele carriers of Taq1A polymorphism of *DRD2* gene have a better therapeutic response [12,13]. The association between AAP response and *DRD2* Ins/Del polymorphism was also suggested by two meta-analyses [14,15]. However, this association was not replicated in a large study with a prospective evaluation of the response [16]. With regard to *DRD2* Taq1A polymorphism, no association between this polymorphism and AAP response was suggested by a meta-analysis of seven positive studies and five negative studies [15]. Two additional negative studies were published following this previously mentioned meta-analysis [16,17]. Overall, the interpretation of these conflicting results remains difficult due to allelic heterogeneity related to ethnic background. In particular, some authors report an association between A1 allele and some A2 alleles with good response [18,19].

With regard to the *HTR2A* gene, several lines of evidences suggest the implication that this gene in AAP response variability in SCZ. Indeed, it has been shown that the -1438G>A polymorphism in *HTR2A* influences the transcription levels [20]. In addition, previous studies also showed that the T102C polymorphism of this gene plays an important role in *HT2RA* mediated neurotransmission [21,22]. In connection with therapeutic response, 12 studies analysing the influence of T102C polymorphism of the *HTR2A* gene on AAP response have been published: one reports an association between the C allele and better response [23], another reports an association between T allele and better response [24], and ten studies did not show any association [25–34]. Six studies investigated -1438G>A polymorphism, with two reporting an association between G allele and poor treatment response [35,36], one reporting that the presence of G allele was associated with better response [37], another reporting an association between the AA genotype and negative symptoms improvement [38], and two studies not showing any association with response to AAP [31,39]. Of particular interest for the present work, two independent studies among Indian populations, which reported an association between the *HTR2A* gene (-1438G>A; T102C polymorphisms) and SCZ [40,41]. Among the eight studies that have investigated the role of *HTR2C* gene polymorphism on AAP response, only two have shown an association with AAP treatment response [34,42–48]. *HTR2C* -759C>T is an important genetic polymorphism and reported to affect the its receptor expression [49]. Though two studies have been conducted to evaluate the role of *HTR2C*-759C>T in AAP response, they contradict each other, with one study showing no association with response and another study showed an association with improvement in negative symptoms [34,47].

There are several possible reasons for these conflicting results including AAP treatment heterogeneity, ethnic background disparities, treatment duration, response assessment tools, power of detection (sample size) and outcome criteria as well as the study design (prospective or retrospective assessment of the response). So far, the influence of these polymorphisms on AAP response has not been investigated in South Indian populations, except for one study that analyzed the influence of *DRD2* Taq1A polymorphism on AAP response and another study that investigated the *DRD2* Taq1A

and *HTR2A* (-1438A>G;T102C) polymorphisms with risperidone response among the North-Indian population [50,51].

To further explore the association between *DRD2*, *HTR2A* and *HTR2C* genes polymorphisms and AAP response to antipsychotic medication, we conducted an association study between these candidate genes and treatment response in South Indian populations of patients with schizophrenia treated with risperidone (4-8 mg/day).

METHODS

Patients with schizophrenia (n=320) recruited for the study as per Diagnostic and Statistical Manual for Mental Disorders-V, criteria were recruited for the study from the Department of Psychiatry, Jawaharlal Institute of Post graduate Medical Education and Research (JIPMER), Puducherry, India. All the patients were recruited between December 2013 and August 2015. The study protocol was approved by Institute Ethics Committee (Project No. JIP/IEC/4/2013/189) and after explaining the study procedure, written informed consent was obtained from all the patients or patients' legally acceptable representatives. A total of 320 patients with schizophrenia were recruited for the study. Among the total patients n=211 patients were recruited cross-sectionally, by assessing the clinical global impression improvement (CGI-I) score for antipsychotic response after receiving the risperidone (4-8mg/day) for minimum of 4 weeks and n=109 patients were recruited with prospective assessment. In the prospective study group, patients who have not received any antipsychotic medication for past 30 days and have been prescribed risperidone (4-8mg/day) as their antipsychotic therapy for a minimum of four weeks were recruited for the study. In the prospective group, baseline characteristics, positive, negative and general psychopathology symptoms were assessed using Positive and Negative Syndrome Scale (PANSS) score before starting the therapy and after receiving the risperidone therapy for a minimum of four weeks. Patients who had history of other medical illness, substance abuse, pregnant women, nursing women and patients with age of <18 years were excluded from the study.

Response Assessment

In the cross-sectional study group, clinical global impression-improvement (CGI-I) score of seven-point rating scale was assessed. After adequate trial of risperidone treatment patients with CGI-I score of 1-3 considered as responders and 4-7 considered as non-responders [52].

In the prospective study group, two response assessment criteria were used. The antipsychotic response to risperidone was assessed using PANSS global score to evaluate the early treatment response. A continuous variable "Δ PANSS" defined difference between baseline PANSS score and follow-up PANSS score was used for assessment of patients. Patients were also categorized as responders (who showed more than 20% reduction in PANNS score after four weeks of treatment) and non-responders patients who did not show more than 20% reduction in PANSS score after four weeks of treatment [53].

DNA extraction & genotyping

Five millilitre of blood was collected from each patient to study the genetic polymorphisms in dopamine *DRD2* (-141 C Ins/Del, Taq 1A) and serotonin [*HTR2A* (-1438 A/G, 102 C/T), *HTR2C* -759 C/T] receptor genes. DNA extraction was done using standard phenol-chloroform method and quantified by NanoDrop™ (ThermoFisher). Genotyping for genetic polymorphisms were done using real time thermocycler (ABI Prism 7300) with Taqman® SNP probes for *DRD2* genes rs1799732 Assay ID: 0150250174, rs1800497 Assay ID: C__7486676_10 and *HTR2A* rs6311 Assay ID: C__8695278_10, rs6313 Assay ID: C__3042197_1_ and *HTR2C* rs3813929 Assay ID: C__27488117_10 from Applied Biosystems (Foster City, CA, USA).

Statistical analysis

Demographic characteristics of patient details were expressed as mean ± standard deviation. Hardy-Weinberg equilibrium was tested on genotype frequencies. Chi-square test and Fisher's exact test were used to study the association between genotypes and categories of response to risperidone. Kruskal-Wallis test was used to study the association between the genotypes and Δ PANSS. For bimodal categorical variable, Mann- Whitney U test was used to analyse reduction in PANSS scores between genotypes. All statistical analyses were done with Graph Pad Instat version 3.06.

RESULTS

A total of n= 320 patients with schizophrenia were included for the genotype- phenotype analysis. Among the 320 patients, 109 patients were recruited with prospective assessment and 211 patients were recruited in cross-sectional study group. The PANSS score of prospective study group participants was 91.47±17.71 (mean ±SD) at baseline and after four weeks of risperidone treatment, the PANSS score was 57.96 ± 20.49 (mean ±SD). Categorically, 84 patients were responders (20% reduction on PANSS score) and others 25 patients were non responders. Among the 211 cross-sectional study group participants, 154 were responders and 57 were non-responders to risperidone therapy on CGI-I score. All the responders and non-responder's demographic details were given in Table. I.

Genotypic distributions were in Hardy-Weinberg equilibrium for the *DRD2* Taq1A (n=320, χ^2=0.32, DF=1, p=0.5), the *HTR2A* rs6311 (n=320, χ2=1.3, DF=1, p=0.2), *HTR2A* rs6313 (n=320, χ^2=1.34, DF=1, p=0.2) and the *HTR2C* rs3813929 in female subjects (n=132, χ^2=1.4, DF=1, p=0.2) since this gene is located on X chromosome. During the genotyping of *DRD2* -141 C Ins/Del polymorphism, ten samples were not amplified and were excluded. Due to the low frequency of Del allele, the Del/Del subjects (n=5) were combined with Ins/Del genotype to study the association with antipsychotic response.

No significant association was detected between risperidone response (categorical definition) and *DRD2*, *HTR2A* and *HTR2C* genes polymorphisms (Table. II, IV and V). Similarly, no significant association was detected between the level of response based on the level of reduction of the PANSS score and *DRD2*, *HTR2A* and *HTR2C* genes polymorphisms (Table. III). In post-hoc exploratory analyses, no association was detected between the improvement of positive and negative symptoms and general psychopathology sub scores of PANSS score in relation with candidate genes polymorphisms. (Supplementary Table. I).

DISCUSSION

In the present study, using a prospective assessment of symptom evaluation and using two definitions of response, as well as using CGI-I score response assessment in cross-sectional study group, we have examined the role of the associations of *DRD2* (rs1799732, rs1800497), *HTR2A* (rs6311, rs6313) and *HTR2C* (rs3813929) gene polymorphisms with antipsychotic response among South Indian patients with SCZ. The present study did not find significant influence of the studied polymorphisms on treatment response to risperidone.

Allele frequencies of the *DRD2* and *HTR2A* polymorphisms in the present study were consistent with those reported in other studies of Indian populations. Indeed, with regard to *DRD2* Taq1A polymorphism, in our sample, G allele frequency (0.69) was consistent with those reported by Vijayan *et al* (0.69) in South Indian populations and another study by Kaur *et al* (0.68) in North Indian populations (50,51). For *DRD2* -141 C Ins/Del polymorphism the Ins allele frequency (0.77) could not be compared to other South Indian population with SCZ but consistent with allele frequency of South Indian alcohol dependant patients (0.77) and controls (0.65) [54]. Similarly, another study by Sujitha *et al* reported the allele frequencies of *HTR2A* gene polymorphisms -1438A<G (G-0.56; A-0.44), and T102C (C-0.58; T-0.42) in patients with SCZ from South Indian populations [41] which is consistent with the present study and also consistent with another recent study by Kaur *et al* in which -1438A<G (G-0.59; A-0.41), and T102C (C-0.56; T-0.44) were reported in patients with SCZ from

North Indian populations [51]. To the best of our knowledge no data have been reported on *HTR2C* -759 C>T polymorphism frequency in Indian populations.

Previous studies, two from Japanese, three from Caucasians, one each from Chinese, African American, and Korean populations have found an association between *DRD2* Taq1A polymorphism and antipsychotic response [18,19,31,34,55–58]. However, present study results are consistent with many other studies that did not find an association between these genetic polymorphisms and treatment response to antipsychotics in other ethnic groups [12,13,32,47,59]. In particular, *DRD2* Taq1A and *HTR2A* (-1438A>G;T102C) polymorphisms results are consistent with previous association studies from Indian populations [50,51]. With regard to the DRD2 -141 Ins/Del polymorphism, present study results did not find an association with antipsychotic response and results are consistent with many of the previous studies [19,31,32,34,35,59,60], with exception of few studies in Chinese, Caucasians and African Americans in whom they have reported an association between *DRD2* -141 C Ins/Del polymorphism and antipsychotic response [12,61,62]. In the present study *HTR2A* gene -1438 A/G polymorphism results are consistent with reported previous studies in Japanese, Dutch, and Caucasian populations [31,32,39] and not consistent with a few studies such as studies in Caucasians, Algerian, American and Chinese population in whom they have reported an association [35,36,38,63]. Similarly, *HTR2A* T102C polymorphism results are consistent with many previous studies [25–31,33,34] and not consistent with few studies from Chinese, American, Caucasians, African American, and Korean populations in whom they have reported an association with antipsychotic response [23,36,46,64,65]. So far very few studies have investigated the role of *HTR2C*-759 C/T polymorphism in association with antipsychotic response. In the present study, *HTR2C*-759 C/T polymorphism did not show significant association with antipsychotic response. Present study findings are consistent with previous study by Ikeda *et al* in the Japanese population [34] and inconsistent with Reynolds *et al* who have reported a negative symptom response in the Chinese population [47].

To the best of our knowledge our study is the first to assess these genetic associations in a large sample of South Indian population with the strengths of ethnic homogeneity, treatment homogeneity with the same atypical antipsychotic tested (risperidone) and definitive response criteria with prospective and cross-sectional assessment. However, previous association studies were reported with use of typical antipsychotics (chlorpromazine, haloperidol, bromperidol, fluphenazine, flupentixol), atypical antipsychotics (clozapine, olanzapine, aripiprazole, nemonapride, amisulpride, sulpride), few studies with mixed medications (typical and atypical) and only six studies have reported with risperidone therapy.

Our results deserve several comments with regard to potential weaknesses. First, short term evaluation of response (only four weeks of treatment may be too short to capture the sufficient variance in primary outcome measure. Of note, Kaur *et al* 2017 also detected no association between the *DRD2* Taq1A and *HTR2A* (-1438A>G; T102 C) polymorphisms in association with treatment response to risperidone after 12 weeks of treatment in North Indian populations. Second, in the present study, categorical outcome criteria may appear arbitrary (20% improvement) and outcome was also studied using a continuous definition for the response. However, previous studies have used various response assessment scales with different cut off values and treatment durations to detect the association between genetic polymorphisms and antipsychotic response.

In conclusion, the results obtained from the present study are in line with recent studies by Kaur *et al* and Vijayan *et al* to suggest *DRD2* (rs1799732, rs1800497), *HTR2A* (rs6311, rs6313) and *HTR2C* (rs3813929) genetic polymorphisms are not associated with antipsychotic response. *DRD2*, *HTR2A* and *HTR2C* are the important genes involved in the pharmacodynamics of risperidone and several studies have showed the importance of these genes in antipsychotic response. However, recent evidences indicate the role of epigenetic mechanisms in antipsychotic response. A study by Shi *et al* (2017) showed that methylation status of *CYP3A4* gene has a significant role in response to risperidone therapy. Few studies have also suggested the association of gene expression levels from peripheral blood with antipsychotic response. However, no studies have been conducted to study the methylation Further studies are required to investigate the methylation pattern of promotor regions or

gene regulatory regions for *DRD2, HTR2A, HTR2C* genes and their expression pattern in association with antipsychotic response.

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CONFLICT OF INTEREST

Authors declared no conflicts of interest.

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Tables

Table. I Demographic characteristic of responders and non-responders

Prospective study group			
Parameter	**Responders (n=84)**	**Non-responders (n=25)**	**p value**
Age (Years)	29 ± 8.6	35 ± 10.3	0.002
Height (cm)	167.73 ± 9.74	152.73 ± 10.14	0.0001
Weight (kg)	61.65 ± 12.6	53.27 ± 12.56	0.007
Risperidone dose (mg/day) Median (IQR)	4 (4-6)	4 (4-6)	
Cross-sectional study group			
	Responders (n=154)	**Non-responders (n=57)**	**p value**
Age	36.5 ± 10.2	33.8 ± 10.5	0.09
Height (cm)	160.6 ± 9.3	153.1 ± 9.2	0.001
Weight (kg)	60.6 ± 12	58.95 ± 11.9	0.3
Risperidone dose (mg/day) Median (IQR)	4 (4-6)	4 (4-6)	

Table. II Genotype association tests between *DRD2, HTR2A* and *HTR2C* genes polymorphisms and antipsychotic response to risperidone in the prospective and cross-sectional samples pooled (categorical definition of responders and non-responders)

***DRD2* -141 C Ins/Del (rs1799732)**	**Ins/Ins (n=177)**	**Ins/Del +Del/Del (n=133)**	**Odds ratio (95% CI)**	**p value**
Responders	127	104	0.70 (0.4 - 1.2)	0.2
Non responders	50	29		
Fisher's exact test p<0.05 considered as significant				
***DRD2* Taq1A (rs1800497)**	**AA (n=35)**	**AG (n=132)**	**GG (n=153)**	**p value**
Responders	24	104	110	0.2
Non responders	11	28	43	
χ^2=2.4, DF=2, p<0.05 considered as significant				
***HTR2A* -1438 A>G (rs6311)**	**AA (n=39)**	**AG (n=164)**	**GG (n=117)**	**p value**
Responders	31	126	81	0.2
Non responders	8	38	36	
χ^2=2.7, DF=2, p<0.05 considered as significant				
***HTR2A* T102C (rs6313)**	**CC (n=115)**	**CT (n=165)**	**TT (n=40)**	**p value**
Responders	80	124	34	0.1
Non responders	35	41	6	
χ^2=3.8, DF=2, p<0.05 considered as significant				
***HTR2C* -759 C>T (rs3813929) Females**	**CC (n=65)**	**CT +TT (n=67)**	**Odds ratio (95% CI)**	**p value**
Responders	50	48	1.3 (0.6 -2.8)	0.5
Non responders	15	19		
Males	**C (n=120)**	**T (n=66)**	**Odds ratio (95% CI)**	**p value**
Responders	91	47	1.2 (0.6 -2.4)	0.4
Non responders	29	19		
Fisher's exact test p<0.05 considered as significant				

Table. III Genotype association tests between *DRD2, HTR2A* and *HTR2C* genes polymorphisms and reduction in PANSS score

Gene	SNP (rsID)	PANSS score difference between the genotypes			
DRD2	**-141 C Ins/Del (rs1799732)**	**Ins/Ins (n=54)**	**Ins/Del+ Del/Del (n=45)**		**p value**
	Δ PANSS	33.29±21.03	34.1±19.3		0.8
	Taq1A (rs1800497)	**AA (n=10)**	**AG (N=49)**	**GG (N=50)**	**p value**
	Δ PANSS	26.8±21.7	36.59±20.6	31.82±18.6	0.3
HTR2A	**-1438 A>G (rs6311)**	**AA (n=17)**	**AG(n=55)**	**GG(n=37)**	**p value**
	Δ PANSS	25.94±18.31	36.72±19.5	32.18±20.6	0.12
	T102C (rs6313)	**CC (n=35)**	**CT (n=58)**	**TT (n=16)**	**p value**
	Δ PANSS	32.62±20.6	35.8±19.8	27.06±18.3	0.2
HTR2C	**Females**				
	-759 C>T (rs3813929)	**CC (n=22)**	**CT (n=24)**	**TT (n=3)**	**p value**
	Δ PANSS	36.5±21.83	31.75±18.23	34.33±12.6	0.6
	Males				
	-759 C>T (rs3813929)	**C (n=37)**	**T (n=23)**		**p value**
	Δ PANSS	35.10±21.05	29.78±19.35		0.4

All values expressed as Mean±SD, Kruskal-Wallis test and Mann-Whitney U test p-value <0.05 considered as significant

Table. IV Genotype association tests between *DRD2, HTR2A* and *HTR2C* genes polymorphism and antipsychotic response to risperidone in prospective study group.

***DRD2* -141 C Ins/Del**	**Ins/Ins (n=54)**	**Ins/Del +Del/Del (n=45)**	**Odds ratio (95% CI)**	**p value**
Responders	41	36	0.78 (0.3 - 2.0)	0.8
Non responders	13	9		
Fisher's exact test p<0.05 considered as significant				
***DRD2* Taq1A**	**AA (n=10)**	**AG (n=49)**	**GG (n=50)**	**p value**
Responders	6	40	38	0.3
Non responders	4	9	12	
χ^2=2.25, DF=2, p<0.05 considered as significant				
***HTR2A* -1438 A>G**	**AA (n=17)**	**AG (n=55)**	**GG (n=37)**	**p value**
Responders	12	46	26	0.2
Non responders	5	9	11	
χ^2=2.71, DF=2, p<0.05 considered as significant				
***HTR2A* T102C**	**CC (n=35)**	**CT (n=58)**	**TT (n=16)**	**p value**
Responders	25	47	12	0.5
Non responders	10	11	4	
χ^2=1.18, DF=2, p<0.05 considered as significant				
***HTR2C* -759 C>T Females**	**CC (n=22)**	**CT (n=24) +TT (n=3)**	**Odds ratio (95% CI)**	**p value**
Responders	18	21	1.2 (0.3 -5.2)	1.0
Non responders	4	6		
Males	**C (n=37)**	**T (n=23)**	**Odds ratio (95% CI)**	**p value**
Responders	30	15	2.2 (0.6 -7.5)	0.2
Non responders	7	8		
Fisher's exact test p<0.05 considered as significant				

Table. V Genotype association tests between *DRD2, HTR2A* and *HTR2C* genes polymorphisms and antipsychotic response to risperidone in cross-sectional study group

***DRD2* -141 C Ins/Del**	**Ins/Ins (n=123)**	**Ins/Del (84) + Del/Del (n=4)**	**Odds ratio (95% CI)**	**p value**
Responders	86	67+1	0.68 (0.3 – 1.2)	0.2
Non responders	37	17+3		
	Fisher's exact test p<0.05 considered as significant			
***DRD2* Taq1A**	**GG (n=103)**	**AG (n=83)**	**AA (n=25)**	**p value**
Responders	72	64	18	0.5
Non responders	31	19	7	
	χ^2=1.2, DF=2, p<0.05 considered as significant			
***HTR2A* -1438 A>G**	**GG (n=80)**	**AG (109) + AA (n=22)**	**Odds ratio (95% CI)**	**p value**
Responders	55	80+19	0.7 (0.3 – 1.3)	0.3
Non responders	25	29+3		
	Fisher's exact test, p<0.05 considered as significant			
***HTR2A* T102C**	**CC (n=80)**	**CT (n=107) +TT (n=24)**	**Odds ratio (95% CI)**	**p value**
Responders	55	77+22	0.7 (0.3 – 1.3)	0.3
Non responders	25	30+2		
	Fisher's exact test, p<0.05 considered as significant			
***HTR2C* -759 C>T Females**	**CC (n=43)**	**CT (n=25) +TT (n=15)**	**Odds ratio (95% CI)**	**p value**
Responders	32	16+11	1.4 (0.54 -3.6)	0.6
Non responders	11	9+4		
Males	**C (n=83)**	**T (n=43)**	**Odds ratio (95% CI)**	**p value**
Responders	61	32	0.95 (0.41 -2.21)	1.0
Non responders	22	11		
	Fisher's exact test p<0.05 considered as significant			

Foot notes

Table. III

All values expressed as Mean±SD, Kruskal-Wallis test and Mann-Whitney U test p-value <0.05 considered as significant.

Supplementary Table. I

All values expressed as Mean±SD, Kruskal-Wallis test and Mann-Whitney U test p-value <0.05 considered as significant.