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ORIGINAL PAPER

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5-ht2c receptor and mao-a interaction analysis: no association with suicidal behaviour in bipolar patients

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Abstract The serotonin 2C (HTR2C) receptor has been implicated in suicide-related behaviours, however there are not many studies to date about HTR2C and suicidality. We studied HTR2C haplotypes in suicide attempters, where our sample composed of 306 families with at least one member affected by bipolar disorder. HTR2C (Cys23Ser and a common STR in the promoter) variants were analyzed with respect to attempter status and the severity of suicidal behaviour. The X-linked haplotype analysis in relation to suicide attempt did not reveal any significant association. Furthermore, we performed a particular gene-gene interaction for the X-linked serotonergic genes (HTR2C and MAOA), and found no association among this intergenic haplotype combination and suicidal behaviour in bipolar disorder.

Key words suicide · 5-ht2c · bipolar disorder · MAO-A · X-linked · haplotype

Introduction

Suicidality is a major concern worldwide [32]. Suicide and suicidal behaviour are responsible for considerable morbidity and mortality in bipolar disorder (BD). The lifetime suicide risk is 19% in BD [14]. Between 25 and 60% of bipolar patients make at least one suicide attempt during the course of their illness [5].

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Demographic factors such as sex, age, geography and religious affiliation are known to influence suicide risk [30]. In our own sample of BD patients, suicide attempts were associated with co-morbid substance abuse disorders [6].

In most Western countries females have higher rates of suicidal ideation and behaviour than males, yet mortality from suicide is typically lower for females than for males [4]. The gender paradox of suicidal behavior is a real phenomenon and not a mere artifact of data collection.

Attempted and completed suicide are familiar behaviours with an heritablity of about 40–50% [21]. Genetic factors also affect suicide risk, but the mechanism and magnitude of the genetic contribution is unknown [26].

There is strong neurobiological evidence showing that serotonergic dysfunction is implicated in suicidal behaviours [15, 19]. The serotonin (5-HT) neurotransmitter system regulates anxiety, impulsivity, and aggression [18], and so disturbances in the functioning of the 5-HT system have been hypothesized to influence suicidal behaviour. Several studies have reported altered serotonin system function in people who die by suicide. For example, low concentrations of the serotonin metabolite 5-hydroxyl-indole-acetic-acid (5-HIAA) in cerebrospinal fluid (CSF) have been associated with both suicide attempts [3] and completed suicide [23].

Serotonin (5-HT) acts through at least 18 cloned receptors. Of these, the ones most often linked to suicide are the 5-HT2A, 5-HT1A [20], and more recently, 5-HT2C receptors [22].

The HTR2C is a large gene spanning at least 230 kb [33]. Lappalainen et al. [17] identified a non-synonymous Cys23Ser polymorphism in the first hydrophobic region of the human HTR2C receptor. Regarding suicide, post-mortem studies demonstrated increased binding of the 5HT2 receptor sites in brains of suicide victims [2] but a genetic association study based on two independent samples from

different ethnicities reported no significant differences in HTR2C Cys23Ser between victims and controls [31]. The same variant was not associated with self-harm behaviour in a case-control study [25]. More recently, Serretti et al. [28] found that suicide, anger or aggression-related behaviours are not associated with the HTR2C gene variants.

Of interest is that the gene encoding MAO-A is located on the chromosome X too and previous reports found this gene associated with suicidal behaviour [11, 29].

Notably, the haplotype association analyses of the HTR2C gene should take into account the X-linked status. A haplotype is the combination of chromosomally phased SNPs. The phase is usually unknown and thus a haplotype cannot be regarded as a descriptive measure (as opposed to genotype analyses for single markers). In contrast, hapoltypes do represent inferential measures, meaning that more than one haplotype pair can be assigned with different probabilities in the same individual. Statistical programs such as PHASE can only assign the most probable haplotype pair for each individual on the other hand other programs such as UNPHASED performs a phase unknown analysis applying the EM algorithm. But when a gene is located on chromosome X, the phase is known for males because of their hemizygous condition. However, traditional programs for haplotype analyses in unrelated subjects usually are not designed for X chromosome analysis, limiting the usefulness of haplotype analyses in genes such as the HTR2C gene.

The realization that gender plays an important role in suicidal behaviors holds important implications for genetic research and points out serotonin genes located on the chromosome X (HTR2C and MAOA) as positional candidates for suicidal behaviour. We have already investigated MAOA gene in our bipolar sample [7].

In this study, we have chosen two functional polymorphisms located in the promoter and in the coding region of HTR2C gene.

We investigated a repeat polymorphism [(GT)12-18/(CT) 4-5] [9] within the 5′ flanking region on the gene. This STR in the promoter seems to be functional. In fact Yuan et al. [34] found that different alleles at this locus can influence the gene expression in vitro. The region of these polymorphisms contains a transcription factor binding site [33]. As for the HTR2C coding region, we typed the Ser23Cys (rs6318) polymorphism. This coding SNP was choosen because an in vitro study showed that the Ser23 is more conctitutively active than the Cys23 [24]. No other markers were typed since we based the study on a specific functional hypothesis.

A functional haplotype strategy reported to be useful in the beta2 adrenergic gene has been shown in hypertension, highlighting the role of interaction among functional polymorphisms within a gene in disease susceptibility [10]. Furthermore our group has used a similar haplotype interaction analysis successfully on chromosome 15, where two genes from the same system (CHRM5 and CHRNA7) are located [8]. The goals of the current study are: (1) to investigate the association between HTR2C gene and suicide attempt and severe suicidal behaviour in our bipolar sample; (2) to explore the hypothesis that HTR2C gene and MAOA gene interact to influence the above mentioned outcomes in the same sample. The main focus of this paper was the suicidality dimension however for practical reasons we explored also the bipolar phenotype.

Methods

Subjects

The study population consisted of 312 nuclear families recruited in the Toronto ares with at least one offspring (118 males and 194 females) affected by BD (I or II) according to DSM-IV criteria [1]. The sample investigated mostly comprised of an outpatient population. Whenever possible, siblings were included in the study. Thus, 26 siblings affected by BD and 46 non-affected siblings were included. In addition, 45 first or second-degree relatives (e.g., parents or grandparents) were included where 12 subjects had a lifetime history of BD. Thus, the total sample comprised of 1043 subjects; 350 affected with BD (131 males and 219 females) and 693 non-affected relatives.

The mean age at the time of the interview was 35.36 ± 10.37 SD. Subjects ranged in age from 16 to 67. The mean age at onset for bipolar disorder was 20 ± 7.58 SD, with female subjects comprising 62% of the sample. Eighty-six patients attempted suicide. The SCID-I was administered to all subjects by trained clinical interviewers. Suicidality was assessed on a quantitative scale, with the following order: 1 = thoughts of death, 2 = suicide ideation, 3 = suicide plan, 4 = suicide attempt. Furthermore, we coded 5 as violent attempt based on the higher severity compared with non-violent attempts [27]. Among the bipolar patients, 267 patients had history of suicide ideas or attempts and the mean score for all 350 suicide ideation/behaviour scores was 2.1 ± 1.4. For the attempters, the age of onset of BD was 19.16 ± 8.36 and the mean age at interview was 34.84 ± 11.02.

Our sample of 312 families would have a power ranging from 54.6 to 94.0% considering a heritability for our quantitative trait ranging from 10 to 20%, under an additive model, a significance level of 0.05, an allele frequency for a disease/marker locus of 0.1.

Laboratory

Blood was obtained from all individuals and genomic DNA was extracted using a high salt extraction method [16]. Molecular analysis was performed blind in respect to the diagnosis of the patients. The STR in the HTR2C promoter polymorphism was tested using 50 ng of DNA that was amplified in a 15 μl reaction containing New England Biolabs' 1X buffer, 1 U of Taq-Polymerase, 1.5 mM of $MgCl_2$, 1.3 μM of fluorescent-tagged forward primers and unlabelled reverse primers from Applied Biosystems, and 0.2 mM dNTP from Amersham Pharmacia. The PCR product was diluted 25-fold and run on the ABI Prism 3100 genetic analyzer and analysed using GeneScan Analysis Software Version 3.7 to perform DNA fragment analysis.

A genotyping quality control procedure was not required since these markers are on the chromosome X and the fact that male subjects cannot be heterozygous allowed us to control the quality of the genotyping.

Statistical methods

Our sample included parent-proband triads as well as sibships with affected and unaffected sibling. The families were analyzed with UNPHASED 3.0.5 [12]. When we analyze the suicide attempt as main outcome, only the bipolar patients with at least one suicide attempt life-time were considered affected. This new version of UNPHASED is showing the result of the family association statistics in the attempters as a case-control allele counts with haplotype relative risk (HRR) statistics. However, in this analysis, the number of informative families is limited to the triads where the mother is heterozygous.

Quantitative trait such as suicidality severity score was analyzed incorporating the sex, the age of assessment and presence of addiction in the probands.

When the diagnosis of bipolar disorder was considered as main outcome, the family association test was performed using the new version of UNPHASED that considered the transmitted alleles as cases and untransimtted alleles as controls.

The pairwise linkage disequilibrium (LD) between the STR and Cys23Ser was calculated using the algorithm implemented in the UNPHASED program. Due to some families having more than one bipolar subject, we calculated the non-parametric LOD score to exclude the presence of linkage in this region by MERLIN.

The power analysis was performed using PBAT v3.1 using the default parameter.

Results

The marker heterozygosities were 0.59 and 0.10 for the STR in the promoter and the Cys23Ser polymorphisms, respectively. The most common alleles were the 207 bp for the STR and Cys for the Cys23Ser.

The analysis of attempter status in the bipolar patients by UNPHASED was nonsignificant for both markers when we looked at the global chi-square. The global P values were 0.284 and 0.306 for the STR marker and Cys23Ser, respectively (Table 1). The number of families with heterozygous mothers within the 86 families with suicide attempters was 22 and 6 for the STR and Cys23Ser, respectively. When we incorporated sex, age of assessment and addiction status as covariates we found that the allele 201 bp in the STR showed a trend ($P = 0.076$) for protection against suicide attempt (OR = 0.351; 95%CI = 0.062–1.984) and the allele 207 bp had a trend for increased risk ($P = 0.087$; OR = 2.849; 95%CI = 0.504–16.100).

When we looked at suicidality as continuous variable the global P value for the STR was not significant ($P = 0.347$) as well as the specific allele tests (Table 2). The analysis of the Cys23Ser for quantitative trait was not significant too ($P = 0.946$) (Table 2). The specific allele tests were not significant even though the tests were corrected for age, sex, and addiction.

The transmission test from parents to affected proband yielded a non significant global test ($P = 0.161$) but the specific allele test showed that the 207 bp allele had a trend for risk for bipolar disorder ($P = 0.075$). When we looked at the Cys23Ser marker we found that there was no over-transmitted allele to bipolar subjects ($P = 0.219$).

There were 26 families informative for the linkage analysis using the X-chromosome version of MERLIN. The non-parametric LOD-score was −0.06 ($P = 0.70$) for the STR and −0.13 ($P = 0.80$) for the Cys23Ser, excluding the linkage to bipolar disorder at these loci.

The analysis with the UNPHASED software showed a D' of 0.895 between the STR in the promoter and the Cys23Ser.

Table 1 HTR2C STR (reference allele: 207 bp) and Cys23Ser suicide attempt analysis

Allele	Case	Control	Ca-Freq	Co-Freq	Odds-R	95%Lo	95%Hi	Chisq	*P* value
201	21	18	0.3088	0.3913	0.3511	0.06212	1.984	3.133	0.07671
207	39	23	0.5735	0.5	1	1	1	2.929	0.087
209	7	5	0.1029	0.1087	0.4941	0.04009	6.09	0	1
Cys23	68	41	0.9315	0.8723	1	1	1	1.248	0.264
Ser23	5	6	0.06849	0.1277	0.3333	0.0272	4.082	1.248	0.264

HTR2C STR: Likelihood ratio chisq = 2.514, 2*df*, *P* value = 0.2846; Addiction status confounder effect: *P* value < 0.001; Sex confounder effect: *P* value < 0.001; Age of assessment confounder effect: *P* value < 0.001. HTR2C Cys23Ser: Likelihood ratio chisq = 1.046, *df* = 1, *P* value = 0.3063; Addiction status confounder effect: *P* value = 0.2705; Sex confounder effect: *P* value = 0.0836; Age of assessment confounder effect: *P* value = 0.6288

Table 2 HTR2C STR and Cys23Ser suicidality severity score analysis

Allele	Count	MarFreq	AddVal	95%Lo	95%Hi	Chisq	*P* value
201	154	0.3043	−0.08601	−0.4491	0.2771	1.419	0.2335
207	293	0.5791	0	0	0	0.1344	0.7139
209	43	0.08498	0.391	−0.3725	1.154	1.631	0.2016
211	12	0.02372	0.9004	−1.785	3.586	2.225	0.1358
Cys23	426	0.7245	0.06858	−0.1979	0.335	0.2412	0.6233
Ser23	162	0.2755	0	0	0	0.2412	0.6233

HTR2C STR: Likelihood ratio chisq = 3.303, *df* = 3, *P* value = 0.3472; Addiction status confounder effect: *P* value = 0.9811; Sex confounder effect: *P* value = 0.6092. Age of assessment confounder effect: *P* value = 0.9928. HTR2C Cys23Ser: Likelihood ratio chisq = 0.004, *df* = 1, *P* value = 0.9463; Addiction status confounder effect: *P* value = 0.8555; Sex confounder effect: *P* value = 0.1072; Age of assessment confounder effect: *P* value = 0.5189; AddVal: estimated genetic value for this haplotype

The two-marker analysis showed undertransmission of the haplotype 201-Ser to suicide attempters with a significant specific haplotype test ($P = 0.002$) (Table 3), however after the inclusion of age, sex, and addiction status the global test lost significance ($P = 0.110$).

When we considered the suicide behaviour as a continuous trait, the global P value was not significant ($P = 0.627$), however after the inclusion of the covariates age, sex and addiction the haplotype 201-Ser showed a slight trend ($P = 0.081$) for lower suicidality severity scores (Table 4).

When we looked at risk for bipolar disorder, we found that the 201-Ser combination was associated with the lower risk for being affected ($P = 0.039$; OR = 0.310 95%CI 0.090–1.065), the global P value was not significant ($P = 0.187$).

Finally, considering the haplotype combination of the MAOA-uVNTR and MAOA-941T/G plus the STR and Cys23Ser in HTR2C together, we found that these two genes do not interact in conferring risk for suicide attempt ($P = 0.8789$) (Table 5). The analysis of the suicide quantitative trait showed no significant result as well ($P = 0.889$) (Table 6).

The overall transmission test of the combined HTR2C-MAOA haplotype showed a slight significance ($P = 0.057$) when we considered bipolar disorder as affection status with the haplotype 3rep-G-209-Cys showing a protective effect against bipolar disorder ($P = 0.008$).

Table 3 HTR2C haplotype suicide attempt analysis

Haplotype	Case	Control	Ca-Freq	Co-Freq	Odds-R	95%Lo	95%Hi	Chisq	*P* value
201-Cys23	32.42	19.41	0.2679	0.2623	0.5924	0.1687	2.08	0.1408	0.7074
201-Ser23	5.222	8.312	0.04316	0.1123	0	0	0	9.54	0.00201
207-Cys23	70.47	38.5	0.5824	0.5203	1	1	1	3.153	0.07578
209-Cys23	8.368	6.714	0.06915	0.09073	0.5071	0.04429	5.806	0.2812	0.5959

Likelihood ratio chisq = 6.033, *df* = 3, *P* value = 0.11. Addiction status confounder effect: *P* value < 0.001. Sex confounder effect: *P* value < 0.001. Age of assessment confounder effect: *P* value = 0.995

Table 4 HTR2C haplotype suicidality severity score analysis

Haplotype	Count	MarFreq	AddVal	95%Lo	95%Hi	Chisq	*P* value
201-Cys23	205.8	0.2763	−0.05261	−0.3557	0.2505	0.03913	0.8432
201-Ser23	34.8	0.04671	−0.5547	−1.687	0.578	3.03	0.08171
207-Cys23	416.3	0.5588	0	0	0	0.4476	0.5035
209-Cys23	67.45	0.09053	−0.05058	−0.6615	0.5604	0.002225	0.9624
211-Cys23	14.15	0.019	0.7936	−2.553	4.141	0.7844	0.3758

Likelihood ratio chisq = 2.598, *df* = 4, *P* value = 0.6271. AddVal: estimated genetic value for this haplotype. Addiction status confounder effect: *P* value < 0.001. Sex confounder effect: *P* value = <0.001. Age of assessment confounder effect: *P* value = 0.9948

Table 5 MAOA/HTR2C interaction suicide attempt

Haplotype	Case	Control	Ca-Freq	Co-Freq	Odds-R	95%Lo	95%Hi	Chisq	*P* value
3-2-201-Cys23	10.59	7.884	0.08025	0.06159	0.6548	0.6548	0.6548	0.2218	0.6377
3-2-207-Cys23	18	15.03	0.1363	0.1174	0.9201	0.9201	0.9201	0.1582	0.6908
4-1-201-Cys23	19.43	20.23	0.1472	0.1581	1.54	1.54	1.54	0.4195	0.5172
4-1-207-Cys23	51.78	52.07	0.3922	0.4068	1	1	1	0.03945	0.8426

Likelihood ratio chisq = 0.6758, *df* = 3, *P* value = 0.8789

Table 6 MAOA/HTR2C interaction suicidality severity score analysis

Haplotype	Count	MarFreq	AddVal	95%Lo	95%Hi	Chisq	*P* value
3-1-201- Cys23	12	0.03324	0.02241	−1.244	1.289	0.01381	0.9064
3-1-207- Cys23	17	0.04709	1.055	−0.8083	2.918	2.58	0.1083
3-2-201- Cys23	22	0.06094	0.1426	−0.7286	1.014	0.1227	0.7262
3-2-207- Cys23	57	0.1579	0.08266	−0.4444	0.6097	0.008715	0.9256
4-1-201- Cys23	52	0.144	0.1283	−0.4966	0.7531	0.000296	0.9863
4-1-207-Cys23	130	0.3601	0	0	0	0.2997	0.5841
4-1-209-Cys23	18	0.04986	−0.1099	−1.421	1.201	0.165	0.6846

AddVal: estimated genetic value for this haplotype. Likelihood ratio chisq = 2.31, *df* = 6, *P* value = 0.8891. Referece Haplotype: 4rep-T-207 p-Cys23

Discussion

This study was conducted using four functional markers of serotonergic genes on chromosome X since our aim was to test the association with suicidality considering the interaction between HTR2C and MAOA. Our main findings are that HTR2C markers do not confer risk for suicide attempt in bipolar disorder. The genetic analysis that we performed incorporating the clinical-demographics factors is very valuable since many of the genetic reports published on serotonin genes and suicidality did not take into account these factors, however after the correction we found just a trend with the allele 201 protecting against suicide attempt.

Regarding the haplotype analysis, very few studies have explored the HTR2C haplotype and suicidality mostly because it is located on the X-chromosome. However due to the fact that we have applied a phase unknown approach, the inferred haplotypes in females do not represent the direct allele sequence along the gene.

We looked at the HTR2C haplotypes we found no association with suicide attempt.

The investigation of the severity of suicidal behaviour yielded no significant results even though the quantitative analysis that we performed had the advantage of including all 306 families, enhancing the power of the analysis, included only the 86 families with suicide attempters, enhancing the power of the analysis.

For practical reasons, we have analyzed these markers including the bipolar phenotype mainly to confirm or rule out genetic overlap between suicidal behavior and bipolar disorders. The 207 allele showed an association trend for the risk of bipolar disorder and suicide attempt suggesting a common genetic background for these two phenotypes. The two markers of the HTR2C gene do not influence the risk of bipolar disorder however previous studies have shown that Cys23 allele can be associated with BD [13].

The two markers in the HTR2C are physically far but the D' is moderately high to allow the analysis of haplotypes. Therefore we performed this analysis on both phenotypes (suicidality and bipolar disorder) and we found that the same haplotype showed a consistent trend across all three traits, suggesting genetic homogeneity between bipolar disorder and suicidal behaviour.

The fact that the HTR2C allele and haplotype are showing the same direction in the phenotype explored in this study, even though the tests are not always significant, pointed out the need to investigate this gene in other psychiatric disorders with high risk of suicide and suicide attempt such as major depression disorder and alcoholism to clarify the degree of genetic overlap of suicide across different psychiatric diagnosis.

There are many studies investigating MAOA gene in suicidal behaviour in both mood disorders and schizophrenia, but the interaction between HTR2C and MAOA genes, both located on the X-chromosome, was not previously analyzed in suicidal behaviour until our study. In fact these two genes should be considered not only functional candidates but also positional candidates due to the significant difference in the incidence of suicide and attempted suicide between males and females. The HTR2C and MAOA genes are located on different arms of the X chromosome, however the rationale behind the haplotype analysis is the fact that these genes can interact in determining the function of the serotonergic synapse and the fact that both are located on the sex-chromosome makes this hypothesis very fascinating when we consider phenotypes that are strongly associated with gender. Regarding the epistatic mechanism, one possibility is that the low functioning allele of the HTR2C gene has a balancing effect against the high functioning allele of the MAOA gene, and vice-versa, affecting the frequency of the haplotype combinations between these two genes.

Our interaction analysis was not significant for both suicide attempt and suicidal behaviour severity.

The main strength of this study is that we have applied a family association strategy using the new version of UNPHASED that avoids population stratification by using parental genotypes. We have chosen this software to take advantage of the X-chromosome option and the possibility of including confounding factors in the analysis.

Despite the fact that the overall association study is negative and only trends were shown, the analysis of X-markers in suicidality remains of great interest. This study also proposes an alternative methodological approach to the study of the gene-gene interaction and suggests the inclusion of clinical and demographic variables in the genetic studies of suicidality.

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