



Research paper

The GG genotype of the serotonin 4 receptor genetic polymorphism, rs1345697, is associated with lower remission rates after antidepressant treatment: Findings from the METADAP cohort

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ABSTRACT

Background: Pharmacological studies have yielded valuable insights into the role of the serotonin 4 receptor (HTR4) in major depressive episodes (MDE) and response to antidepressant drugs (AD). A genetic association has been shown between HTR4 and susceptibility to mood disorders. Our study aims at assessing the association between the HTR4 genetic polymorphism, rs1345697, and improvement in depressive symptoms and remission after antidepressant treatment in MDE patients.

Methods: 492 depressed patients from the METADAP cohort were treated prospectively for 6 months with ADs. The clinical outcomes according to HTR4 rs1345697 were compared after 1 (M1), 3 (M3), and 6 (M6) months of treatment. Mixed-effects logistic regression and adjusted linear models assessed the association between rs1345697 and 17-item Hamilton Depression Rating Scale (HDRS) score improvement and response/remission.

Results: Over the 6 months of treatment, mixed-effects regressions showed lower improvements in HDRS scores (Coefficient=1.52; Confident Interval (CI) 95% [0.37–2.67]; $p = 0.009$) and lower remission rates (Odds Ratio=2.0; CI95% [1.0–4.1]; $p = 0.05$) in GG homozygous patients as compared to allele A carriers.

Limitations: The major limitations of our study are the uncertainty of the rs1345697 effect on HTR4 function, the substantial drop-out rate, and the fact that analysis is not based on randomization between polymorphism groups.

Conclusions: In our study, patients who were homozygous carriers of the variant G of the HTR4 rs1345697 had lower depressive symptoms improvement and 2-fold lower remission rates after antidepressant treatment as compared to allele A carriers. Randomization study should be done to confirm these results.

1. Introduction

Major depressive disorder (MDD) is the main cause of disability worldwide (Jaffe et al., 2019), affecting around 350 million individuals.

However, antidepressants, the main treatment, have insufficient efficacy in the treatment of major depressive episodes (MDE) in both short (Trivedi et al., 2006) and long term (Rush et al., 2006). Among factors involved in treatment efficacy, genetic variants affecting

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drug-metabolizing enzymes such as CYP2C19 or CYP2D6 are known to interfere with treatment response, especially when taking selective serotonin reuptake inhibitors (SSRI) or serotonin-noradrenaline reuptake inhibitors (SNRI) (Caudle et al., 2017; Hicks et al., 2015; Molden and Jukić, 2021; Quaranta et al., 2017). In addition, it would be useful to identify biological factors, including biomarkers that predict antidepressant treatment efficacy (Ozomaro et al., 2013) and, particularly, remission, which is the optimal treatment outcome (Zimmerman et al., 2006). Recently, a predictive algorithm for SSRI clinical outcomes in MDD was developed using a multiple omics research strategy that identified genes such as *TSPAN5*, *ERICH3*, *DEFB1*, and *AHR* (Nguyen et al., 2021). Among novel genes to evaluate, the serotonin type 4 receptors (HTR4) may be candidates.

Indeed, the HTR4, metabotropic Gs-protein coupled receptors, are expressed in brain areas associated with stress and emotion, including the amygdala, the nucleus accumbens, and the hippocampus (Agrawal et al., 2019; Bockaert et al., 2008; Vidal et al., 2014). Recent findings have indicated that targeting the serotonin 4 (5-HT₄R) receptors may constitute a new way to treat anxiety and depression (Faye et al., 2020; Mendez-David et al., 2014; Samuels et al., 2016). Preclinical and clinical data support a role of HTR4 in depression and anxiety. *HTR4* knockout mice show increased depressive-like and anxiety-like behaviours (Amigó et al., 2016), and the depressive behavior of anhedonia in rats is associated with a downregulation of HTR4 in the hippocampus (Bai et al., 2014). Two clinical studies assessed the role of HTR4 in mood disorders. One Japanese case-control study reported polymorphisms in the splice variant region of the *HTR4* gene associated with unipolar depression (Ohtsuki et al., 2002). The second study, a Spanish post-mortem case-control study, showed a higher HTR4 density in the frontal cortex and caudate nucleus of depressed violent suicide victims in comparison to control subjects with no history of psychiatric disease (Rosel et al., 2004). However, such postmortem studies are not able to assess whether the association is related to depression or suicide. In addition, decreased striatal 5-HT₄ receptor binding is associated with risk for familial depression (Madsen et al., 2014). Within the hippocampus in humans, HTR4 levels were inversely correlated with cognitive function in memory test performance (Haahr et al., 2013).

Furthermore, preclinical findings demonstrate a putative benefit of HTR4 signaling modulation in treating anxiety and/or depressive symptoms, with a shorter onset of action when using HTR4s agonists (Compan et al., 2004, 2004; Faye et al., 2020; Lucas, 2009; Lucas et al., 2007; Mendez-David et al., 2014; Pascual-Brazo et al., 2012).

In humans, two completed, but not yet published, clinical studies (ClinicalTrials.gov) were conducted to evaluate the effects of an HTR4 agonist, prucalopride, on emotional processing and neural activity (NCT03572790) and on emotional processing and non-emotional cognition (NCT03863366). To the best of our knowledge, only a genome-wide association study (GWAS) (Uher et al., 2010) in 706 European patients from the GENDEP project (Genome-based therapeutic drugs for depression) assessed antidepressant treatment response and *HTR4* genetic polymorphisms. Patients from this GWAS were treated for 12 weeks either by escitalopram ($n = 394$) or nortriptyline ($n = 312$), and the *HTR4* rs1345697 genetic polymorphism was the strongest associated marker in the *HTR4* gene for the nortriptyline group, although it did not reach statistical significance and was not assessed after long-term treatment. To date, and to our knowledge, there are no elements allowing us to specify the implication of this intronic genetic polymorphism on the functionality of the receptor.

Patients treated for MDD may receive many different classes of antidepressants. Antidepressants act by modulating serotonin and/or other monoamines, such as noradrenaline and dopamine, in the synaptic cleft in different ways. None of them are known to interact with HTR4, as determined by their mechanism of action (monoamine oxidase inhibition, serotonin transporter (SERT) and/or norepinephrine transporter (NET) blockade) and by their lack of affinity for this specific serotonin receptor subtype as defined in the NIMH Psychoactive Drug Screening

Program Ki database (Roth et al., 2000). Moreover, whatever the antidepressant strategies used, including electroconvulsive therapy, the main pharmacological effect is a marked increase in serotonergic transmission (Bliez and El Mansari, 2013).

Thus, our study aimed to assess the association of the *HTR4* (rs1345697) polymorphism with depressive symptoms improvement after 6 months of antidepressant treatment, using Hamilton Depression Rating Scale-17 (HDRS) score reduction and remission as the main outcomes, after 6 months of antidepressant treatment in predominantly European patients with a current MDE.

2. Material and methods

2.1. Patients and design

The study sample comprised patients from the METADAP (Do Antidepressants Induce Metabolic Syndromes) cohort (ClinicalTrials.gov NCT00526383) (Corruble et al., 2015). Over a four-year period, from November 2009 to March 2013, this 6-month prospective, real-world treatment, multi-center study was conducted in 6 psychiatric care settings in France. Six hundred and twenty-four in- or out-patients with a major depressive episode (MDE), requiring the beginning of antidepressant treatment, as a monotherapy, were enrolled. Among them, 492 provided a DNA sample for genotyping.

Eligible patients were aged 18–65 years and had a current MDE diagnosis in the context of MDD and a minimum depression score on the 17-item Hamilton Depression Rating Scale (HDRS) of 18, corresponding to moderate and severe depression (Zimmerman et al., 2013).

Patients were not included if they presented with psychotic symptoms, bipolar, psychotic or eating disorders, current substance abuse or dependence, unstable medical conditions, organic brain syndromes, pregnancy, or were breast-feeding. Patients with a history of antipsychotic or mood stabilizer treatment the month before inclusion, and/or for four months or more during the year preceding inclusion, were not included.

The choice of antidepressant drug and its dose was left to the psychiatrist's discretion. Polytherapy with other antidepressants, antipsychotics, or mood stabilizers was not allowed. To treat symptoms like insomnia or anxiety, benzodiazepines were tolerated at the minimum effective dose and for the minimum duration.

The study followed international ethics standards and was approved by the local Ethics Committee. All participants provided a written informed consent.

The patients were clinically evaluated by their trained psychiatrist at baseline (M0) and one month (M1), three months (M3), and six months (M6) later. Patients' ethnicities were determined according to the place of birth and the ethnicity of the two parents of each patient.

2.2. Depressive symptoms improvement after antidepressant treatment

The Hamilton Depression Rating Scale-17 (Hamilton, 1960) score was rated by trained clinicians at baseline, and 1 (M1), 3 (M3), and 6 (M6) months after the beginning of antidepressant treatment to assess depressive symptoms improvement. To minimize inter-rater reliability and reliability over time, all recruiting psychiatrists were trained by the same senior psychiatrist with two independent rating sessions. Antidepressant response was defined by a decrease in the total HDRS score of at least 50% from baseline to follow-up. A total HDRS score ≤ 7 defined remission (Rush et al., 2006). The Clinical Global Impression Efficacy Index (CGI-E), rated with a symmetrical (4×4) matrix of drug effect and side effects, is a ratio of current therapeutic benefit to severity of side effects (Guy, 1976).

2.3. Genotyping

At baseline, 5 mL of whole blood was collected. Genomic DNA was

extracted from circulating blood leukocytes using Puregene Blood Kits (Gentra Systems) according to the manufacturer's protocol (Qiagen) and cryopreserved at -20°C . The *HTR4* genetic polymorphism (rs1345697) was genotyped using TaqMan allelic discrimination with the ABI Prisms 7900HT Sequence Detection System (Life Technologies) as previously described (Coulbault et al., 2006; Taranu et al., 2017). The sequence of interest was amplified using the following forward primer: 5'-TGCTATGTATTTCATATGGGAAGCAG-3' and reverse primer 5'-TCACAACCACCTTTTATCCCACTAACTAC-3'. Allele A (reference allele) was detected using a 5'-GAGTTCAATTTTGAA-CATGT-3'-VIC-fluorescent probe. Variant allele (G) was detected using the 5'-GTTCAATTTTGACATGTTA-3'-FAM-fluorescent probe. In addition, the *HTR4* rs1345697 polymorphism (NM_001040173.2(*HTR4*): c.27–12413A>G) is located in an intronic region of the *HTR4* gene. Genotypic analyses were run blind to clinical evaluations.

2.4. Statistical analysis

Statistical analyses were performed using Stata v.13, and all tests were two-tailed. An alpha level of 5% was considered as statistically significant. Our initial hypothesis was that the rs1345697 genetic polymorphism might have an impact on antidepressant treatment response, without prejudging its direction.

Hardy-Weinberg equilibrium was assessed using the chi-square test.

The *HTR4* genetic polymorphism (rs1345697) was the independent variable, and GG carriers were compared to allele A carriers (AA and AG patients). Bivariate analyses were performed to compare socio-demographic and baseline MDD clinical characteristics (sex, age, weight, marital status, educational level, smoking status, recurrent MDD, previous antidepressant treatment, antidepressant class, HDRS scores) using chi-square tests for categorical variables and independent t-tests for continuous variables. All patients were analyzed even though marital or smoking status was missing for some patients.

A mixed-effects linear regression model was used to compare HDRS scores, while mixed-effects logistic regression models were used to assess response and remission rates over time, considering each time point of evaluation. These mixed-effects models were adjusted for age, sex, ethnicity. These variables were chosen *a priori* as potential confounders, regardless of the possible differences between genotype groups at baseline.

Post hoc analyses were performed in the event of a significant genotype effect. Linear and logistic regressions were carried out at M1, M3, and M6, with HDRS and remission as explicative variables and the *HTR4* genetic polymorphism (rs1345697: GG versus A-carriers) as the independent variable. The same potential cofounders used in mixed-effects linear regression models, among demographic and clinical variables (i. e., age, sex, ethnicity) were controlled in these multivariate analyses.

Chi-square tests were used to compare frequency tables between genotype groups and SSRI/SNRI use. Mixed-effects models for HDRS scores, response, and remission rates over time, were also used to examine the interaction between genotype groups and SSRI/SNRI use.

In addition, mixed-effects models for HDRS scores, response, and remission rates over time were performed among SSRI and SNRI treated patients.

Moreover, to assess potential differences in adverse events between genotype groups, adverse events severity, rated with the CGI-E after 3 and 6 months of antidepressant treatment, were compared using chi-square tests.

The association between baseline characteristics used as covariates in the mixed-effects models and *post hoc* analyses and the dropout rates were assessed using chi-square tests for categorical variables (sex, ethnicity) and independent t-tests for continuous variables (age, HDRS). The proportion of study completers among *HTR4* genetic polymorphism groups (rs1345697: GG versus A-carriers) was compared using Pearson chi-square tests.

3. Results

3.1. Sample characteristics

Among the 624 patients included in the METADAP cohort, 492 had a DNA sample available for genotyping. The 492 patients were mainly women (69%, $n = 337$) with a mean age of 45.4 ± 13.3 years and a high educational level (defined as having at least a university-level degree) in 48% ($n = 236$). At baseline, their mean HDRS score was 24.8 ± 4.9 . Seventy-five percent ($n = 367$) of patients had received a previous antidepressant treatment and 73% ($n = 359$) had a recurrent MDE, determined by a clinical exam. At baseline, most of the patients (89%, $n = 437$) required hospitalization. During the study, most of the patients were discharged, with 47% ($n = 173$), 13% ($n = 35$), and 5% ($n = 11$) hospitalized after one, three, and six months, respectively. After discharge, some patients were re-hospitalized when their psychiatrist deemed it necessary. During the study, they were mainly treated (Table II.) with SSRIs (including paroxetine, escitalopram, and citalopram) and SNRIs (mostly venlafaxine) in 43% ($n = 208$) and 40% ($n = 193$) of cases, respectively. Six percent ($n = 31$) of patients were treated with tricyclic antidepressants (mainly clomipramine) and 9% ($n = 46$) with other antidepressants (mainly mirtazapine). The classes of antidepressants used were not significantly different between the genotype subgroups (i. e., AA-AG versus GG).

The Pearson chi-square test showed no significant difference in SSRI/SNRI use ($p = 0.316$) or in adverse events severity after 3 ($p = 0.083$) and 6 months ($p = 0.924$) between genotype groups.

Mixed-effects models showed no interaction between genotypes groups and SNRI/SSRI use for HDRS scores ($p = 0.586$), response rates ($p = 0.593$), and remission rates ($p = 0.517$) over time.

Their socio-demographic and clinical characteristics according to rs1345697 genotype groups are presented in Table I. At baseline, allele A-carriers (AA and AG) and homozygous variant genotype (GG) groups did not differ for socio-demographic, MDD clinical characteristics, antidepressant drug class, and HDRS scores.

One hundred and thirty-five (27%) were homozygous wild type (AA), 243 (49%) were heterozygous (AG), and 114 (23%) were homozygous variant (GG). The genotype distribution showed no significant deviation ($p = 0.6923$) from Hardy-Weinberg equilibrium. Ninety percent ($n = 447$) of the studied samples were European (defined as two European parents according to a self-report). In our sample, the observed allelic frequencies were 52% for the A allele and 48% for the G allele. The allelic frequencies in the general population of the genome Aggregation Database (gnomAD) (Karczewski et al., 2020) are 51% (A allele) and 48% (G allele). In Non-Finnish Europeans, these frequencies are 52% and 48% for A and G alleles, respectively. The allelic frequencies in our whole sample, comprising 90% Europeans, were thus comparable to those in Europeans of gnomAD. Since the minor allele is G, GG homozygotes were compared to carriers of the A allele.

3.2. Depressive symptoms improvement after antidepressant treatment

The dropout rates were 24%, 45%, and 58% after 1 month, 3 months, and 6 months, respectively. The main reasons for dropout were an antidepressant change (36%), the use of unauthorised drugs (7%), or a loss to follow-up (51%). Thus, HDRS scores were available for 374, 271, and 207 patients after 1, 3, and 6 months, respectively. Dropout rates were not statistically associated with the baseline characteristics used as covariates in the statistical analyses (age: $p = 0.4663$; HDRS score: $p = 0.1118$; sex: $p = 0.209$; ethnicity: $p = 0.284$). The number of completers among the *HTR4* genetic polymorphism groups (rs1345697: GG versus A-carriers) was not statistically different ($p = 0.966$).

Overall results do not change when the models are unadjusted, but the standard error is smaller with adjusted covariates.

Lower HDRS score improvement in the homozygous variant (GG) carriers ($M0 = 25.0 \pm 4.8$; $M1 = 14.7 \pm 6.7$; $M3 = 14.3 \pm 7.5$; $M6 =$

Table I

Patient characteristics at baseline according to *HTR4* (rs1345697) genetic polymorphism groups and Hamilton Depression Rating Scale-17 (HDRS-17) scores.

	Whole sample 492	AA-AG 378	GG 114	p
Patients (n)				0.692
Women [% (n)]	69 (337)	52 (255)	17 (82)	0.368
Age (years) (<i>m</i> ± <i>sd</i>)	45.4 ± 13.3	45.7 ± 13.3	44.5 ± 13.2	0.431
Weight (kg) (<i>m</i> ± <i>sd</i>)	66.9 ± 15.1	66.9 ± 15.2	66.9 ± 14.8	0.990
Marital status [% (n)]				0.691
Single	29 (142)	22 (106)	7 (36)	
Married	48 (235)	37 (182)	11 (53)	
Divorced	18 (88)	14 (71)	4 (17)	
Widowed	5 (25)	4 (18)	1 (7)	
High educational level [% (n)]	48 (236)	37 (184)	11 (52)	0.990
Smoking status [% (n)]				0.235
No smoking	49 (243)	37 (184)	12 (59)	
Ceased smoking	38 (186)	29 (141)	9 (45)	
Active smoking	13 (62)	11 (53)	2 (9)	
Recurrent MDD [% (n)]	73 (359)	57 (279)	16 (80)	0.526
Previous antidepressant treatment [% (n)]	75 (367)	58 (283)	17 (84)	0.909
Antidepressant class [% (n)]				0.755
TCA	6 (31)	5 (23)	2 (8)	
SSRI	43 (208)	34 (165)	9 (43)	
SNRI	40 (193)	30 (145)	10 (48)	
Others	9 (46)	7 (36)	2 (10)	
QIDS-C (<i>m</i> ± <i>sd</i>) M0	23.1 ± 5.3	22.6 ± 5.5	23.6 ± 5.1	0.348
HDRS-17 (<i>m</i> ± <i>sd</i>)				
M0	24.8 ± 4.9	24.8 ± 4.9	25.0 ± 4.8	0.607
M1	14.5 ± 7.1	14.4 ± 7.1	14.7 ± 6.7	0.743
M3	12.1 ± 7.3	11.4 ± 7.1	14.3 ± 7.5	0.0058
M6	10.4 ± 7.9	9.7 ± 7.3	13.0 ± 9.3	0.0131

n: number; m: mean; sd: standard deviation; MDD: major depressive disorder; TCA: tricyclic antidepressant; SSRI: selective serotonin reuptake inhibitors; SNRI: serotonin and norepinephrine reuptake inhibitors; QIDS-C: Quick Inventory of Depressive Symptomatology scale clinician rated; HDRS-17: Hamilton Depression Rating Scale 17-items; M0: baseline; M1: after 1 month; M3: after 3 months; M6: after 6 months.

13.0 ± 9.3) as compared to the allele A carriers (M0 = 24.8 ± 4.9; M1 = 14.4 ± 7.1; M3 = 11.4 ± 7.1; M6 = 9.7 ± 7.3) was observed in a linear mixed-effects model (coefficient = 1.52; confident interval (CI) 95% [0.37–2.67]; $p = 0.010$) (Fig. 1, Table III). In a multiple linear regression post-hoc analysis, homozygous GG carriers had significantly higher HDRS scores after 3 ($p = 0.0062$) and 6 ($p = 0.0097$) months of antidepressant treatment. They were not significantly different at baseline and after 1 month of antidepressant treatment.

Lower remission rates (Fig. 2A) in the GG carriers [M1: 16% ($n = 13$), M3: 19% ($n = 12$), and M6: 37% ($n = 17$)] as compared to allele A carriers [M1: 21% ($n = 61$), M3: 32% ($n = 68$), and M6: 47% ($n = 75$)] were observed with a logistic mixed-effects model (OR = 2.0; CI95% [1.0–4.1]; ($p = 0.05$) (Table III). No specific sub-time effects were identified (M1: OR=0.72; CI95% [0.36–1.37], $p = 0.343$; M3: OR=2.08; CI95% [0.93–4.76]; $p = 0.078$), and M6: OR=1.79; CI95% [0.80–4.00]; $p = 0.16$).

Response rates at M1, M3, and M6, respectively, were 46% ($n = 37$), 46% ($n = 29$), and 54% ($n = 25$) among the homozygous variant (GG) carriers and 40% ($n = 115$), 60% ($n = 125$), and 71% ($n = 114$) among the allele A carriers subgroup (Fig. 2B.). The mixed-effects model showed no statistically significant association between the *HTR4* rs1345697 polymorphism and the response rates over time (Table III.).

In the subgroups analysis, the mixed-effects model showed no statistically significant association between the *HTR4* rs1345697

polymorphism and HDRS, response and remission rates over time for SSRI treated patients. (Table III).

As in the whole sample, the mixed-effects models showed lower HDRS score improvement (Coefficient=1.8, CI95% [0.08–3.52], $p = 0.04$) and lower remission rates (OR=2.7, CI95% [1.0–7.1], $p = 0.04$) in the GG carriers and no statistically significant association for the response rates in the subgroup of SNRI treated patients (Table III.).

4. Discussion

We show here for the first time the association between the *HTR4* rs1345697 polymorphism and depressive symptoms improvement and remission after antidepressant treatment. As seen with the mixed-effects model, GG carriers had significantly lower HDRS scores improvement and lower remission rates than allele A carriers. As measured with the HDRS scores, the magnitude of the effect might appear modest, however these encouraging results are worth further exploration and replication with multiple omics research strategies, such as those described by Nguyen et al. (Nguyen et al., 2021). In addition, based on our clinical experience with patients, a 3.7-points decrease in HDRS score begins to be clinically significant. Interestingly, the effect size of the association is important since the GG carriers had two-fold lower remission rates than allele A carriers.

To our knowledge, this is the first study to explore the association between the *HTR4* rs1345697 genetic polymorphism and the response after antidepressant treatment in a large cohort of mostly European MDE patients. Our initial hypothesis was based on a GWAS (Uher et al., 2010) of the European GENDEP population, in which, among more than 500,000 genetic variants, this genetic polymorphism was reported as the strongest marker among 41 *HTR4* genetic polymorphisms detected associated with nortriptyline response, although it did not reach genome-wide statistical significance and was not significantly associated with symptoms improvement and remission over 12 weeks. Indeed, our *post hoc* analyses indicated that a difference in HDRS improvement between genotypes was not observed in the earlier assessment one month after treatment, but only after 3 and 6 months of treatment.

As far as we know, the *HTR4* rs1345697 genetic polymorphism has never been studied in such a naturalistic study, especially in patients mainly treated with SSRIs and SNRIs (mainly citalopram and venlafaxine). Our results support what was highlighted by Uher et al. (Uher et al., 2010) as the effect of *HTR4* rs1345697 genetic polymorphism on HDRS score improvement and remission is different between SSRI (mainly citalopram) and SNRI treated patient groups. Indeed, in their study comparing a group of patients treated either by escitalopram ($n = 394$) or nortriptyline ($n = 312$), the *HTR4* rs1345697 was identified as a potential marker associated with response in the nortriptyline group. As a matter of fact, despite not being an SNRI, nortriptyline acts by inhibiting both serotonin and norepinephrine reuptake. Given the lack of affinity of antidepressants for *HTR4*s as defined in the NIMH Psychoactive Drug Screening Program Ki database (Roth et al., 2000) and the fact that the main pharmacological effect, regardless of the class of antidepressant treatment used, is a marked increase in serotonergic transmission (Blie and El Mansari, 2013), the reasons for this difference remain unknown. We can hypothesize that the difference might not be due to serotonin but to an indirect mechanism. To our best knowledge no interaction between *HTR4* and norepinephrine has been described. However, an interaction between *HTR4* and dopamine levels exists (Guo et al., 2020; Parga et al., 2007). Moreover, this difference might be due to efficacy and safety profiles that are different from one class of antidepressants to another, rather than to a questionable influence on the *HTR4*.

The *HTR4* rs1345697 is an intronic genetic polymorphism and could not explain a modification of the *HTR4* protein. We could hypothesize that this polymorphism is in linkage disequilibrium with another polymorphism in the 5'-flanking region, or an exonic region, of the *HTR4* gene, that could affect transcription. Indeed, several single-nucleotide

Table II
Patient's treatment characteristics according to *HTR4* (rs1345697) genetic polymorphism groups.

	HTR4 AA-AG mean dosage +/- sd (mg)			HTR4 GG mean dosage +/- sd (mg)		
	M1	M3	M6	M1	M3	M6
TCA						
Clomipramine	113.9 +/- 42.2 n = 17	135.5 +/- 26.8 n = 13	151.9 +/- 25.5 n = 10	190.9 +/- 31.3 n = 4	227.7 +/- 44.4 n = 3	227.7 +/- 44.4 n = 3
Amitriptyline	25 n = 1	0	0	0	0	0
SSRI						
Paroxetine	25.2 +/- 7.5 n = 36	25.6 +/- 7.4 n = 18	27.3 +/- 7.8 n = 15	31.7 +/- 16.1 n = 6	32.0 +/- 19.2 n = 6	20 +/- 0 n = 2
Fluvoxamine	150 +/- 33.3 n = 3	150 +/- 50 n = 2	150 +/- 50 n = 2	0	0	0
Fluoxetine	24.3 +/- 8.7 n = 14	23.3 +/- 8.3 n = 12	22.5 +/- 8.7 n = 8	20 +/- 0 n = 4	20 +/- 0 n = 3	20 +/- 0 n = 3
Escitalopram	14.3 +/- 5.5 n = 43	15.3 +/- 6 n = 30	15.5 +/- 5.5 n = 22	15.4 +/- 5.4 n = 9	13.9 +/- 5 n = 6	13.1 +/- 5 n = 6
Citalopram	24.5 +/- 7.4 n = 31	25.8 +/- 10.1 n = 25	25.3 +/- 12.0 n = 18	25.6 +/- 7.4 n = 9	28.9 +/- 7.9 n = 9	30 +/- 6.7 n = 6
Sertraline	47.8 +/- 15.3 n = 7	83.3 +/- 37.5 n = 3	37.5 +/- 11.1 n = 2	105.0 +/- 36 n = 5	137.5 +/- 18.8 n = 4	125.0 +/- 25.0 n = 2
SNRI						
Duloxetine	73.3 +/- 17.8 n = 9	77.1 +/- 19.6 n = 7	75 +/- 20 n = 6	67.5 +/- 11.2 n = 4	60 +/- 0 n = 3	60 +/- 0 n = 2
Venlafaxine	162.0 +/- 56.5 n = 109	187.8 +/- 66.4 n = 81	184.9 +/- 61.8 n = 63	179.9 +/- 58.7 n = 33	183.5 +/- 60.8 n = 25	172.2 +/- 55.2 n = 18
Milnacipran	100 n = 1	100 n = 1	0	0	0	0
Others						
Mianserin	10 n = 1	10 n = 1	0	90 n = 1	90 n = 1	90 n = 1
Mirtazapine	21.6 +/- 9.4 n = 16	24.5 +/- 10.4 n = 10	25.7 +/- 12.2 n = 6	25 +/- 6.7 n = 3	30 n = 1	0
Tianeptine	37.5 n = 1	0	0	0	0	0
Agomelatin	36.1 +/- 12.3 n = 9	32.1 +/- 10.2 n = 7	33.3 +/- 11.1 n = 3	25 +/- 0 n = 2	25 n = 1	25 n = 1
Iproniazid	137.5 +/- 62.5 n = 4	150 +/- 66.7 n = 3	175 +/- 50 n = 3	0	0	0
ECT	4	1	0	0	1	0
rTMS	1	1	0	0	0	0

n: number; sd.: standard deviation; M1: first month; M3: third month; M6: sixth month; TCA: tricyclic antidepressants; SSRI: selective serotonin reuptake inhibitors; SNRI: serotonin and norepinephrine reuptake inhibitors; ECT: electroconvulsive therapy; rTMS: Repetitive Transcranial Magnetic Stimulation.

polymorphisms (SNP) have been described in the gene but, until now, the 5'-flanking region sequence was not available because the GWAS GENDEP analyzed only some exonic SNPs. It is important to note that in pharmacogenetics, many others intronic genetic polymorphisms are considered relevant with a phenotypic response (e.g., CYP2C19×17 and citalopram (Sim et al., 2006), CYP3A5×3 and tacrolimus, or CYP2D6×4 and antidepressants (Ingelman-Sundberg and Sim, 2010)). Thus, an extensive analysis of the 5'-flanking region and a functional characterization study of the protein would greatly help to understand the implication of the *HTR4* rs1345697 in remission.

If *HTR4* exhibits a wide distribution [for review (Vidal et al., 2014)], it is mainly located in limbic areas, including the hippocampus. Serotonin, whose levels are increased by antidepressants, binds to the *HTR4* G protein-coupled receptor, which stimulates the cAMP-PKA signaling pathway, resulting in the expression of genes involved in neuroplasticity. All signaling cascades reported to be affected by *HTR4* stimulation are involved in remodeling of neuronal morphology and activity-dependent structural plasticity [for review (Vidal et al., 2014)]. Moreover, we previously showed that *HTR4* contributes to the effects of SSRI on adult hippocampal neurogenesis, including in the maturation of newborn neurons (Mendez-David et al., 2014). We could assume that *HTR4* does not participate in the initial phases of the antidepressant response, but helps to consolidate the response present after one month of antidepressant treatment through its role in cerebral plasticity. *HTR4* could therefore contribute to the overall remission by giving a boost to avoid relapse. Recent data suggested that *HTR4* agonists are also effective prophylactics against stress (Chen et al., 2020).

An altered plasticity might explain the lack of symptoms improvement after the first month of antidepressant treatment in GG carriers. Indeed, onset of action of antidepressant treatment takes time and its effects on outcome, as seen here, appear after 3 or 6 months. In addition, promising results are emerging from studies of *HTR4* agonists used in humans to treat depression and cognitive impairment (for review (Murphy et al., 2020)). Among the latter, the cognitive effects of prucalopride have been characterized (Murphy et al., 2019), suggesting a role for *HTR4* agonists as an adjunct to SSRIs to improve cognitive function.

Our study has several strong points. Firstly, it was a naturalistic study conducted in everyday psychiatric care settings. Such a real-life setting provides good insights into patients' outcomes. Secondly, it had a long-term follow-up (6 months), with multiple evaluations at baseline, 1, 3, and 6 months. Thirdly, it was conducted in a large homogeneous sample in terms of diagnosis: MDD with a current MDE requiring an antidepressant drug treatment. Most patients were female, which is typical of the reality of MDD.

However, our study has several limitations. Firstly, the treatment was left to the psychiatrist's discretion according to his clinical assessment in a non-randomized, naturalistic, open way. However, this method allows for the assessment of rs1345697 in "real life" conditions. Secondly, many patients dropped out prematurely, with an attrition rate of 44% and 57% at 3 and 6 months of treatment, respectively. Nonetheless, these rates are close to those observed in other naturalistic cohorts like STAR*D (Trivedi et al., 2006). Furthermore, we used mixed-effects models, which are robust in the case of attrition. As a matter of fact, using mixed-effects models, we analyzed our data in a

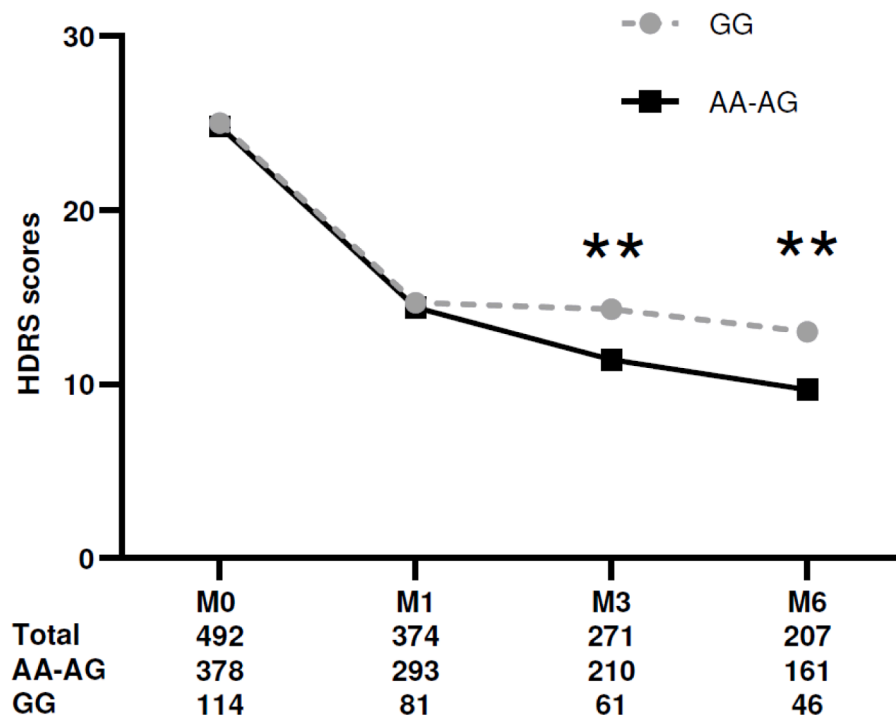


Fig. 1. *HTR4* (rs1345697) genetic polymorphism affects Hamilton Depression Rating Scale-17 (HDRS-17) score evolution after antidepressant treatment [at baseline (M0), 1 (M1), 3 (M3), and 6 (M6) months (** $p < 0.01$ GG versus AA-AG genotype)].

Table III

Mixed-effects regression showing the relationship between *HTR4* rs1345697 genetic polymorphism and Hamilton Depression Rating Scale-17 (HDRS-17), and response and remission rates, over the 6 months of the METADAP study in the whole sample (A.) of patients and in the subgroups of patients treated with SSRI (B.) and SNRI (C.).

A. Whole sample Baseline Characteristics	HDRS		Response				Remission		
	Coefficient	[95% CI]	p	Odds ratio	[95% CI]	p	Odds ratio	[95% CI]	P
<i>HTR4</i> rs1345697	1.52	0.37 2.67	0.009	1.4	1.0 2.2	0.09	2.0	1.0 4.1	0.05
Sex	0.68	-0.24 1.61	0.15	1.3	0.9 1.8	0.12	1.7	1.0 2.9	0.03
Age	-0.0007	-0.034 0.033	0.97	1.0	0.995 1.010	0.27	1.0	0.99 1.03	0.36
Ethnicity	-0.29	-1.07 0.49	0.47	0.8	0.6 1.1	0.16	0.8	0.6 4.4	0.95
B. SSRI		Response				Remission			
Baseline Characteristics	Coefficient	[95% CI]	p	Odds ratio	[95% CI]	p	Odds ratio	[95% CI]	p
<i>HTR4</i> rs1345697	1.02	-0.80 2.84	0.27	1.2	0.6 2.2	0.68	1.8	0.6 5.4	0.33
Sex	0.49	-0.026 0.68	0.49	1.1	0.7 1.8	0.74	1.2	0.5 2.5	0.70
Age	0.02	-0.025 0.068	0.37	1.0	0.999 1.036	0.04	1.0	0.99 1.04	0.26
Ethnicity	-0.25	-1.06 0.558	0.54	0.9	0.7 1.1	0.32	0.8	0.6 1.2	0.34
C. SNRI		Response				Remission			
Baseline Characteristics	Coefficient	[95% CI]	p	Odds ratio	[95% CI]	p	Odds ratio	[95% CI]	p
<i>HTR4</i> rs1345697	1.8	0.08 3.52	0.04	1.6	0.9 3.1	0.13	2.7	1.0 7.1	0.04
Sex	1.30	-0.13 2.73	0.07	1.8	1.1 3.0	0.03	2.6	1.3 5.3	0.009
Age	-0.04	-0.10 0.017	0.17	1.0	0.97 1.01	0.51	1.0	0.97 1.03	0.88
Ethnicity	0.57	-3.0 4.15	0.75	0.9	0.2 3.6	0.90	0.5	0.1 3.4	0.52

OR: odds ratio; CI: confidence interval; SSRI: selective serotonin reuptake inhibitors; SNRI: serotonin and norepinephrine reuptake inhibitors.

long format. Therefore, a patient with missing data at a specific visit/time-point would not result in a complete loss of information for that patient, and an average estimation could still be calculated based on the remaining non-missing data points. Thirdly, our study did not include a specific assessment for anxiety disorders and cognition. Fourthly, anxiolytic treatment was allowed, but not exhaustively reported and did not allow for taking this variable into account for statistical analyses. However, these treatments were used primarily during the first month of antidepressant treatment; their mandatory prescription duration is limited to a maximum of 12 weeks. Thus, although this variable should not impact the results after 3 and 6 months, it may still be a confounding factor. In addition, other potential confounders, such as family psychiatric history, known to contribute to MDD liability, were not available in our study. Lastly, as discussed above, the intronic

position of the rs1345697 polymorphism, and the lack of data regarding its influence on receptor function, is a limitation. This could suggest that another polymorphism in this region is also correlated with response and remission in people with MDD.

In conclusion, this study explored for the first time the association of the *HTR4* genetic polymorphism (rs1345697) and remission after antidepressant treatment in a large cohort of predominantly European depressed patients. In our sample, this polymorphism was associated with antidepressant remission, with ancestral allele carriers presenting with greater remission over time. Additional studies remain to be undertaken to determine if rs1345697 plays a role in *HTR4* structure and to characterize its functional aspects. Beside such functional studies, a study comparing two groups, differing according to *HTR4* rs1345697 genetic polymorphism, randomized to either nortriptyline or

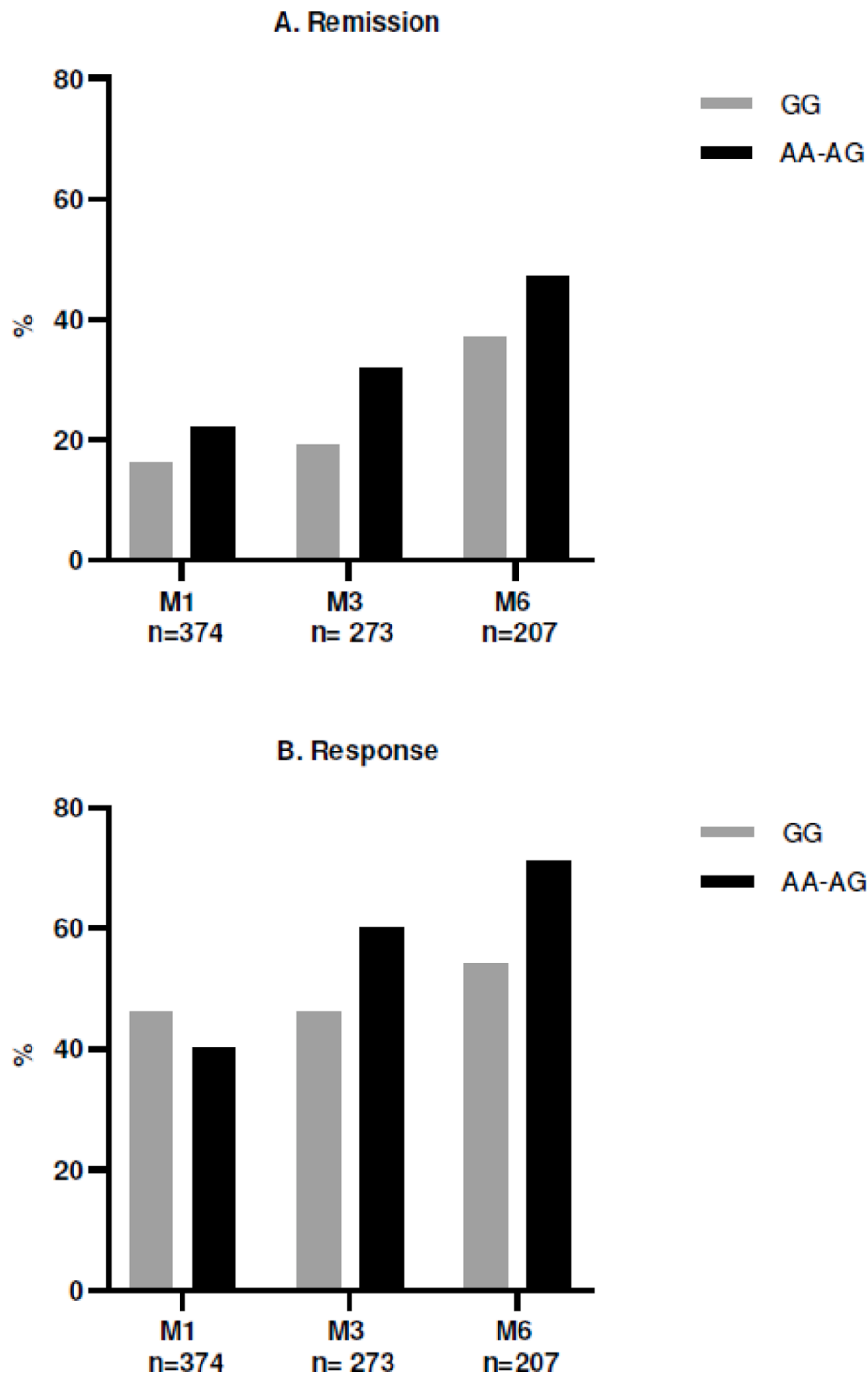


Fig. 2. Remission (2A) and response (2B) rates after antidepressant treatment at 1 (M1), 3 (M3), and 6 (M6) months: AA-AG versus GG genotypes of the *HTR4* (rs1345697) genetic polymorphism.

escitalopram, would provide more clarity regarding the relevance of the polymorphism to treatment outcome.

This might help to understand the underlying mechanisms involved in treatment response and improve outcome in MDD patients.

5. Contributors

VP drafted the manuscript with input from all authors. EC, LB and CV designed the study. RC, AAT, FG, BF and EC included patients in the study. CV analyzed samples and oversaw the biobank storage. KEA conducted the statistical analysis of the data. All authors approved the

final version of the manuscript.

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Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Declaration of Competing Interest

Laurent Becquemont: investigator for Antisense Therapeutics, Alnylam Pharmaceuticals, PregLem SA, Ionis Pharmaceuticals, Novartis, Auris Medical, MedDay Pharma, Gilead Sciences, Actelion. Received consulting fees from Sanofi, Pfizer and Servier; lecture fees from Genzyme and Pfizer. Bruno Fève received lecture fees from Sanofi, Amgen, Lilly, Novonordisk and MSD, and grants from MSD and Viiv Healthcare for his laboratory. Denis J. David serves as a consultant for Lundbeck, Inc., and receives compensation from Lundbeck. Indira Mendez-David, Denis J. David are named on nonprovisional patent applications for the prophylactic use of RS67333 against stress-related psychiatric disorders, Céline Verstuyft serves as a consultant and receives compensation from Galapagos and Novartis. Abd El Kader Ait Tayeb, Kenneth Chappell, Romain Colle, Emmanuelle Corruble, Khalil El-Asmar, Florence Gressier, Hugo Herrero and Vianney Poinssignon have no conflict of interest to disclose.

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