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Éric Deflesselle

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Polymorphismes génétiques du TRKB, caractéristiques cliniques et réponse après traitement antidépresseur dans le trouble dépressif unipolaire

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Thèse présentée et soutenue au Kremlin-Bicêtre, le 2 février 2021, par

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TABLES DES MATIERES

FIGURES.....	6
TABLEAUX.....	7
LISTE DES ABREVIATIONS	8
1 INTRODUCTION	11
1.1 Définition.....	11
1.2 Épidémiologie	11
1.3 Médecine générale et dépression	12
1.4 Prise en charge.....	12
1.5 Hétérogénéité de la dépression et biomarqueurs.....	13
1.6 Neurogenèse	13
1.7 La génétique et la pharmacogénétique	14
2. PLAN DE LA THESE.....	16
2 METHODES	16
2.1 LA COHORTE METADAP	16
2.2 POPULATION.....	17
2.2.1 Critère d'inclusion	17
2.2.2 Critères d'exclusion	17
2.3 TRAITEMENTS	18
2.3.1 Traitements évalués	18
2.3.2 Traitements tolérés	18
2.4 RECUEIL DE DONNÉES.....	19
2.4.1 Données générales.....	19
2.4.2 Données liées à la dépression	19
2.4.3 Données génétiques.....	19
2.5 STATISTIQUES.....	20
2.5.1 Données d'analyse	20
2.5.2 Tests statistiques.....	22
2.6 DESCRIPTION GENERALE DE LA COHORTE	22
3 RESULTATS	24
3.1 ASSOCIATION ENTRE DES POLYMORPHISMES DU TRKB ET LES CARACTERISTIQUES CLINIQUES DE LA DEPRESSION.....	24
3.1.1 Article 1	25
3.1.2 Résumé.....	26
3.1.3 Introduction.....	27
3.1.4 Matériel et Méthodes	29

3.1.5	Résultats	31
3.1.6	Discussion	35
3.1.7	Conclusion.....	38
3.2	REPONSE AUX ANTIDEPRESSEURS	39
3.3	ASSOCIATION ENTRE DES POLYMORPHISMES DU TRKB ET LA RÉPONSE APRÈS TRAITEMENT ANTIDÉPRESSEUR	40
3.3.1	Article 2	41
3.3.2	Résumé	42
3.3.3	Introduction.....	43
3.3.4	Méthodes.....	44
3.3.5	Résultats	47
3.3.6	Discussion	55
3.3.7	Conclusion.....	58
3.3.8	Article 3	59
3.3.9	Résumé	60
3.3.10	Introduction.....	61
3.3.11	Patients et Méthodes.....	63
3.3.12	Résultats	66
3.3.13	Discussion	70
3.3.14	Conclusion.....	71
3.4	INTERACTION ENTRE LES POLYMORPHISMES DU TRKB ET LES CARACTERISTIQUES CLINIQUES DE LA DEPRESSION SUR LA REPONSE APRES TRAITEMENT ANTIDEPRESSEUR	72
3.4.1	Introduction.....	73
3.4.2	Méthode	73
3.4.3	Résultats	75
3.4.4	Discussion	81
3.4.5	Conclusion.....	83
4	DISCUSSION	84
4.1	RAPPELS DES PRINCIPAUX RESULTATS	84
4.2	LIMITES.....	85
5	CONCLUSION ET PERSPECTIVES	86
6	REFERENCES	89
7	ANNEXE.....	100

FIGURES

Figure 1 : Plan de la thèse	16
Figure 2 : Diagramme de flux de la cohorte METADAP	23
Figure 3 : Etape 1 de la thèse	24
Figure 4 : Association entre le SNP rs2289656 du TRKB et les tentatives de suicide récentes.....	34
Figure 5 : Etape 2 et 3 de la thèse	39
Figure 6 : Etape 2 de la thèse	40
Figure 7 : Etape 3 de la thèse	72
Figure 8 : Biomarqueurs et caractéristiques cliniques étudiés pour la réponse/rémission sous antidépresseurs : principaux résultats.....	84

TABLEAUX

Tableau 1 : Description des SNP étudiés et notation	21
Tableau 2 : Caractéristiques cliniques et démographiques en fonction des polymorphismes génétiques du TRKB étudiés	33
Tableau 3 : Caractéristiques des études incluses	46
Tableau 4 : Les SNP du BDNF associés avec une efficacité des antidépresseurs.....	48
Tableau 5 : Les haplotypes du BDNF associés avec une efficacité des antidépresseurs.	52
Tableau 6 : Les SNP du TRKB associés avec une efficacité des antidépresseurs	53
Tableau 7 : Etudes publiées sur les SNP du TRKB et la réponse après traitement par antidépresseurs chez des patients déprimés	62
Tableau 8 : Répartition allélique des huit polymorphismes du TRKB et équilibre d'Hardy-Weinberg dans notre cohorte de patient déprimé.....	64
Tableau 9 : Caractéristiques cliniques et démographiques à l'inclusion en fonction des polymorphismes génétiques du TRKB étudiés.....	68
Tableau 10 : Efficacité des antidépresseurs après 1, 3 et 6 mois de traitement en fonction des polymorphismes génétiques du TRKB étudiés	69
Tableau 11 : Influence des caractéristiques cliniques sur la réponse, rémission et HDRS après traitement antidépresseur.....	77
Tableau 12 : Significativité (p) des interactions entre les polymorphismes du TRKB et les caractéristiques cliniques de la dépression sur la réponse, rémission et HDRS après traitement antidépresseur	79
Tableau 13 : Significativité (p) des interactions entre les polymorphismes du TRKB et les caractéristiques cliniques de la dépression sur la réponse, rémission et HDRS après traitement antidépresseur	80

LISTE DES ABREVIATIONS

ADN (ou DNA en anglais): Acide désoxyribonucléique
ANSM : Agence Nationale de Sécurité du Médicament et des Produits de Santé
AMM : Autorisation de Mise sur le Marché
AP-HP : Assistance Publique - Hôpitaux de Paris
ARNm : Acide Ribonucléique messenger
BDNF : Facteur neurotrophique issu du cerveau
CGI : Impressions Cliniques Globales
CHU : Centre Hospitalier Universitaire
CNIL : Commission Nationale de l'Informatique et des Libertés
CNVs : Variation du nombre de copies CYP2D6 : Cytochrome P450 2D6
EDC (ou MDE en anglais) : Episode Dépressif Caractérisé
DSM-IV-TR : Manuel diagnostique et statistique des troubles mentaux version IV texte révisé
DSM-5: Manuel diagnostique et statistique des troubles mentaux version 5 ECT : Electroconvulsivothérapie
GAD1 : Glutamate decarboxylase 1
GRIK2 : Récepteurs kaïnate ionotrope au glutamate 2 (
GRIN1 : Récepteurs N-Methyl D-Aspartate ionotrope au glutamate 1
GRM7 : Récepteurs du glutamate métabotrope
GWAS : Etude d'association pangénomique
HAMD : Echelle de Dépression de Hamilton
HR : Rapport des risques
IC (ou CI en anglais) : Intervalle de confiance
IRM (ou MRI en anglais) : Imagerie par Résonance Magnétique
ISRS (ou SSRI en anglais) : Inhibiteur Sélectif de Recapture de la Sérotonine
ISRN (ou SNRI en anglais) : Inhibiteur Sélectif de Recapture de la Sérotonine et de la Noradrénaline
IMI (ou TCA (tricyclic antidepressant) en anglais) : Imipraminique
KO : Knock Out
MINI : Mini entretien international neuropsychiatrique
NGS : Séquençage de Nouvelle Génération
NNT : Nombre de Sujets Nécessaires de Traiter
OMS : Organisation Mondiale de la Santé
OR : Rapport de cotes (ou Odds Ratio en anglais)
PCR : Réaction en chaîne par polymérase
PHRC : Programme Hospitalier de Recherche Clinique
PNTR75 : Récepteur à Neurotrophine p75
SLC6A4 : Transporteur de sérotonine et porteur de soluté dépendant du sodium 6A4
SNP : Polymorphisme Nucléotidique Simple
SPM : Statistical Parametric Mapping
TDU (ou MDD en anglais) : Trouble Dépressif Unipolaire
TPH2 : Tryptophan hydroxylase 2
TRKB : Récepteur Tyrosine-Kinase B
5-HT : Sérotonine
5-HTTLPR : Région promotrice liée au transporteur de la sérotonine

RESUME

Introduction : Les études sur l'Animal et l'Homme montrent que le Récepteur Tyrosine-Kinase B (TRKB), principal récepteur du Brain Derived Neurotrophic Factor (BDNF), est impliqué dans le trouble dépressif unipolaire (TDU) et le mécanisme d'action des antidépresseurs. Les variations génétiques du TRKB pourraient être un biomarqueur des caractéristiques cliniques de l'épisode dépressif caractérisé (EDC) et prédire la réponse après traitement antidépresseur.

Notre objectif est d'examiner l'association entre des polymorphismes génétiques du TRKB et les caractéristiques cliniques de la dépression et la réponse après traitement antidépresseur chez des patients déprimés.

Méthodes : Les données originales de ce travail sont issues de la cohorte METADAP. Il s'agit d'une cohorte prospective ouverte et naturaliste, multicentrique incluant 624 patients présentant un EDC dans le cadre d'un trouble dépressif caractérisé unipolaire et nécessitant l'introduction d'un traitement antidépresseur. Nous avons évalué 8 polymorphismes nucléotidiques simples (SNP) du TRKB, rs1778933, rs1187352, rs2289658, rs2289657, rs2289656, rs3824519, rs56142442 et rs1439050 ainsi que les caractéristiques cliniques : les antécédents de tentative de suicide (TS) (ancienne (>1 mois) ou récente (<1 mois)), les antécédents d'EDC et de traitement par antidépresseur et la sévérité de l'EDC actuel. La réponse après traitement antidépresseur était évaluée après 1, 3 et 6 mois de traitement.

Résultats : 1) Le génotype CC du rs2289656 est associé à une augmentation des TS récentes. 2) La revue de la littérature met en évidence une association entre rs10868223, rs11140778, rs1565445 et rs1659412, et réponse après traitement antidépresseur. 3) Nos données ne mettent pas en évidence d'association significative entre les 8 SNP du TRKB et la réponse après traitement antidépresseur. 4) Nous n'avons pas mis en évidence d'interactions entre SNP et caractéristiques cliniques sur la réponse après traitement.

Conclusion : Les patients homozygotes CC pour le rs2289656 présentent deux fois plus de tentatives de suicide récentes que les porteurs de l'allèle T. Aucune autre association n'est observée entre les 8 SNPs du TRKB et les caractéristiques cliniques de l'EDC d'une part et la réponse après traitement antidépresseur d'autre part.

MOTS CLES : réponse après traitement antidépresseur, polymorphisme génétique, pharmacogénétique, TRKB, caractéristique clinique, épisode dépressif caractérisé

ABSTRACT

Introduction: Animal and human studies show that the Tyrosine Kinase B Receptor (TRKB), the main receptor for Brain Derived Neurotrophic Factor (BDNF), is involved in major depressive disorder (MDD) and the antidepressant mechanism of action. Genetic variations in TRKB could be a biomarker of the clinical features of the major depressive episode (MDE) and predict the response after antidepressant treatment.

Our objective is to examine the association between TRKB genetic polymorphisms and clinical features of depression and response after antidepressant treatment in depressed patients.

Methods: The original data for this work are from the METADAP cohort. This is a prospective, open, naturalistic, multicenter, prospective cohort including 624 patients with MDE in a mood depressive disorder requiring the introduction of naturalistically prescribed antidepressant therapy. We evaluated 8 single nucleotide polymorphisms (SNPs) of TRKB, rs1778933, rs1187352, rs2289658, rs2289657, rs2289656, rs3824519, rs56142442 and rs1439050 as well as their clinical characteristics : history of (past (>1 month) or acute (<1 month)) suicide attempt (SA), history of MDE and antidepressant treatment and severity of current MDE. Response after antidepressant treatment was assessed after 1, 3 and 6 months of treatment.

Results: 1) The CC genotype of rs2289656 is associated with an increase of acute SA. 2) The literature review showed an association between rs10868223, rs11140778, rs1565445 and rs1659412 and response after antidepressant treatment. 3) Our data do not show a significant association between the 8 SNPs of TRKB and response after antidepressant treatment. 4) We did not demonstrate any interactions between SNPs and clinical features on post-treatment response.

Conclusion: Homozygous CC patients for rs2289656 had twice as many recent suicide attempts as T-allele carriers. No other association is observed between the 8 SNPs of TRKB and clinical features of MDE on the one hand and antidepressant response on the other hand.

KEY WORDS: ANTIDEPRESSANT RESPONSE, GENETIC POLYMORPHISM, PHARMACOGENETICS, TRKB, CLINICAL FEATURES, MAJOR DEPRESSIVE EPISODE

1 INTRODUCTION

1.1 Définition

La maladie dépressive ou trouble dépressif unipolaire (TDU) est un trouble mental caractérisé par la succession d'épisodes dépressifs caractérisés (EDC). Un EDC est caractérisé par une tristesse accompagnée de symptômes comme une faible estime de soi, une perte d'intérêt ou de plaisir, des troubles du sommeil et de l'appétit ainsi que des comportements suicidaires (DSM-5 traduction française). Ces symptômes ont, par définition, un retentissement marqué sur la vie du sujet (dans les domaines affectif, social et professionnel).

1.2 Épidémiologie

L'EDC est un trouble fréquent avec une prévalence annuelle de 6 % et une prévalence vie entière de 20 %. Il touche deux fois plus la femme que l'homme. L'âge médian pour le 1^{er} épisode est de 25 ans [1].

Il est à l'origine d'un certain nombre de complications majeures en termes de santé publique. Tout d'abord socio-économiques : Le TDU est l'une des 3 premières causes d'incapacité en 2017 dans le monde selon l'Organisation Mondiale de la Santé (OMS) [2]. C'est un facteur de risque de nombreuses maladies telles que le diabète, les maladies cardio-vasculaires et respiratoires [3].

Parmi les complications majeures dues au TDU, il y a le suicide. Le TDU augmente de 5 fois le risque de faire une tentative de suicide [4]. Entre 5.6 et 6.8 % des personnes avec un TDU mourront par suicide et jusqu'à 13.7 % avec un TDU sévère [5]. Au-delà du suicide, Le TDU augmente le risque de maladies telles que le diabète, l'obésité, les accidents vasculaires cérébraux (AVC), l'infarctus du myocarde ou la démence [6]. En raison de ces complications et en particulier l'insuffisance cardiaque, le TDU augmente de 50 % la mortalité [6,7].

1.3 Médecine générale et dépression

Le médecin généraliste (MG) est le 1^{er} recours pour le diagnostic et la prise en charge du TDU. Parmi les patients ayant une détresse psychologique, 60 % consultent un médecin généraliste et seulement 10 % un psychiatre [8]. Plusieurs causes sont avancées : la stigmatisation des personnes ayant des pathologies mentales mais aussi l'accès à un psychiatre [9]. Certains travaux dans les pays en voie de développement ont montré l'aspect bénéfique de leur prise en charge par les médecins généralistes pour pallier ce manque d'accès aux spécialistes [9].

Selon une étude en France, 9.1 % des patients du médecin généraliste ont un diagnostic d'EDC [10]. Cela représenterait au moins 25 % des patients consultant pour un renouvellement de traitement [11]. Le MG fait face à plusieurs défis. Bien que le patient avec un EDC utilise plus souvent le système de soin, celui-ci est 3 fois moins observant pour des raisons telles que le doute sur l'efficacité des antidépresseurs, un plus grand isolement et des troubles de la mémoire présents dans cette maladie [11]. Au niveau du diagnostic, selon une méta-analyse, ce médecin ne détecterait que 50 % des cas avec une spécificité de 81 % [12]. Enfin, au niveau de la prise en charge, 60 % de ces patients recevraient un traitement antidépresseur et la moitié un anxiolytique. Pour plus de la moitié des patients qui reçoivent un traitement antidépresseur, celui-ci n'est pas indiqué [10]. Développer des outils au service du médecin généraliste est un enjeu majeur pour améliorer le diagnostic, l'observance et prise en charge du TDU.

1.4 Prise en charge

Les traitements de référence de l'EDC selon l'HAS sont des antidépresseurs d'emblée dans les EDC modérés à sévères. Cela est laissé à l'appréciation du médecin dans le cas d'EDC d'intensité légère [13,14].

Le praticien a à sa disposition cinq classes d'antidépresseurs : Les inhibiteurs sélectifs de la recapture de la sérotonine (ISRS), augmentant la concentration de sérotonine dans la synapse en empêchant sa recapture dans le neurone présynaptique, les inhibiteurs de la recapture de la sérotonine et de la noradrénaline (IRSNa), inhibant la recapture de la noradrénaline et de la sérotonine, les antidépresseurs tricycliques (TCA) empêchant la recapture de divers neurotransmetteurs, y compris la sérotonine, la noradrénaline et la dopamine, les inhibiteurs de monoamine oxydase (IMAO), augmentant la concentration en

monoamines en inhibant les enzymes de dégradation de ces substances, et les «autres antidépresseurs» dont les mécanismes d'action sont variés.

La stratégie thérapeutique médicamenteuse est de proposer un traitement antidépresseur de la classe ISRS ou IRSNa en première intention du fait de la meilleure tolérance de ces médicaments. Les traitements de deuxième intention, tels que les TCA, les IMAO et les autres antidépresseurs, ne sont utilisés qu'en cas de réponse insatisfaisante ou d'EDC d'intensité particulièrement sévère [13].

1.5 Hétérogénéité de la dépression et biomarqueurs

Le TDU se présente de manière hétérogène en termes de caractéristiques cliniques (sévérité, récurrence, idées suicidaires, etc.) mais aussi au niveau de la réponse au traitement. Après quatre semaines de traitement par antidépresseurs, seul un tiers des patients déprimés présente une réponse thérapeutique satisfaisante, un tiers une réponse partielle et un tiers une absence de réponse au traitement [15].

Certaines de ces caractéristiques cliniques, telles que la sévérité, les antécédents d'EDC ou de prise d'antidépresseur, semblent permettre de prédire la réponse après traitement antidépresseur dans le TDU [16-22].

Néanmoins, la prévision des caractéristiques cliniques de la dépression et la réponse après traitement antidépresseur reste un défi pour le clinicien. Pourtant, cette question est cruciale car elle a un impact sur le pronostic immédiat (risque suicidaire), à moyen terme (réponse au traitement et comorbidités) ou à long terme (récurrence et mortalité) [6]. L'utilisation de biomarqueurs pourrait permettre de comprendre cette hétérogénéité et aider le médecin généraliste dans sa prise en charge.

1.6 Neurogenèse

La neurogenèse (i.e. la naissance de nouveaux neurones notamment au niveau hippocampique [23]) est impliquée dans la physiopathologie de la dépression [24,25] ainsi que dans le mécanisme d'action des médicaments antidépresseurs [26,27]. Chez les animaux avec un modèle de dépression, la neurogenèse est diminuée. Celle-ci est stimulée

par les antidépresseurs et inversement l'activation de la neurogenèse induit un effet antidépresseur [26-32].

Le « Tyrosine Kinase Receptor B » (TRKB), principal récepteur du BDNF (Brain Derived Neurotrophic Factor), une neurotrophine, est partie prenante de la neurogenèse. Son activation induit la neurogenèse (naissance de nouveaux neurones), l'arborisation neurale et la synaptogenèse [26,33].

Il est présent sur les membranes pré-synaptique et post-synaptique des neurones principalement au niveau du système nerveux central.

Il serait impliqué dans la dépression avec une présence post-mortem réduite au niveau hippocampique chez les personnes avec un TDU [34] et certaines de ses variations génétiques auraient une influence sur le risque de dépression [35].

Il intervient aussi dans les mécanismes de réponse aux traitements antidépresseurs [36]. Le TRKB est activé par les antidépresseurs chez la souris [37]. Chez des souris sans TRKB dans les cellules hippocampiques, Li met en évidence une inefficacité des antidépresseurs en termes comportemental et cellulaire (neurogenèse) et, réciproquement selon Liu, l'utilisation d'un agoniste du TRKB a une activité antidépressive chez la souris [38,39]. Chez l'homme, trois études ont évalué l'impact des polymorphismes génétiques du TRKB sur la réponse après traitement antidépresseur chez le patient déprimé. Au total, 155 SNP du TRKB ont été étudiés [40-42].

1.7 La génétique et la pharmacogénétique

La génétique est l'étude de la variabilité interindividuelle de la séquence de l'ADN génomique responsable d'une variabilité phénotypique. La pharmacogénétique est l'étude de la génétique sur la pharmacologie, c'est-à-dire de l'influence de la génétique sur l'effet des traitements.

La part d'héritabilité génétique dans l'EDC est estimée selon les études de 36 à 66 % [43,44]. Les techniques d'exploration génétique sont actuellement en plein développement. Elles apportent des informations utiles pour le diagnostic de certaines maladies, mais aussi pour anticiper l'efficacité ou la tolérance des traitements. Certains tests sont d'ailleurs recommandés voire exigés par la FDA (Food and Drug administration) ou l'EMA

(European Medicines Agency) avant l'introduction de certains traitements en pratique courante [45].

La pharmacogénétique est déjà utilisée pour déceler les caractéristiques graves telles que le cancer du sein ou le lymphome, pour choisir le traitement adéquat dans le cancer du sein ou du poumon, la leucémie lymphoïde chronique ou pour la réponse à un traitement spécifique tel que le clopidogrel ou l'abacavir (pour le VIH) [46].

Dans la dépression, certaines variations génétiques comme celles présentes sur les gènes du GRIN1 ou GRM7 sembleraient être associées à un risque plus grand de dépression, tandis que d'autres influeraient sur la tolérance aux antidépresseurs (CYP2D6) ou sur la réponse après traitement antidépresseur (5-HTTLPR, TPH2, GRIK2 GAD1 ou SLC6A4) [47,48]. Dans une méta-analyse, Rosenblat associe une meilleure réponse après traitement antidépresseur en termes d'efficacité et de tolérance dans la dépression si le choix de l'antidépresseur est guidé par la pharmacogénétique [49]. La génétique pourrait être un biomarqueur de la réponse après traitement antidépresseur.

Notre hypothèse est que les variations génétiques du TRKB pourraient influencer sur les caractéristiques cliniques du TDU ainsi que sur la réponse thérapeutique après traitement antidépresseur.

L'objectif de ce travail est d'évaluer l'influence des polymorphismes génétiques du TRKB sur les caractéristiques cliniques de la dépression et la réponse après traitement antidépresseur chez des patients ayant un EDC.

Dans un premier temps, chez des patients avec un EDC, nous évaluerons l'influence de la génétique du TRKB sur les caractéristiques cliniques du TDU. Dans un deuxième temps, nous évaluerons l'influence de la génétique du TRKB (seul et en association avec les caractéristiques cliniques) sur la réponse thérapeutique après traitement par antidépresseurs.

2. PLAN DE LA THESE

Dans un premier temps, nous présentons les résultats de l'analyse de l'influence des polymorphismes génétiques du TRKB sur les caractéristiques cliniques du TDU. Dans un second temps, nous présentons les résultats de l'analyse de l'influence des polymorphismes génétiques du TRKB sur la réponse thérapeutique en prenant en compte les caractéristiques cliniques du TDU.

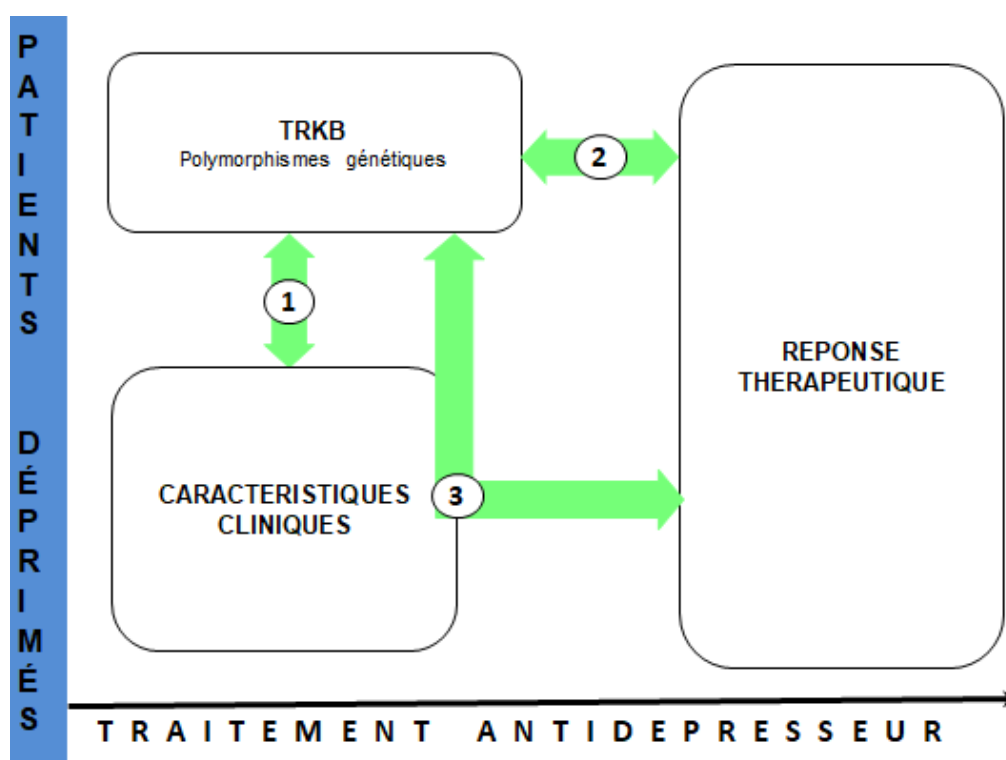


Figure 1 : Plan de la thèse

Légendes ; TRKB : Récepteur Tyrosine-Kinase B.r

2 METHODES

2.1 LA COHORTE METADAP

Nos recherches ont porté sur la cohorte METADAP, une étude financée par deux Programmes Hospitaliers de Recherche Clinique (PHRC) National accordés en 2006 et 2011 (Pr Corruble) [50]. L'analyse de la DNA-thèque a été financée par un PHRC régional accordé en 2010 (AOR 10 071) (Dr Gressier).

Cette base regroupe dans une cohorte prospective, ouverte, multicentrique et dont la prise en charge est faite de manière naturaliste avec un suivi de 6 mois, 624 patients inclus de 2009 à 2013 présentant un épisode dépressif caractérisé au moment de l'inclusion dans le cadre d'un trouble dépressif unipolaire et nécessitant l'introduction d'un traitement antidépresseur.

L'étude a été enregistrée auprès de l'Agence Française de Sécurité du Médicament et des Produits de Santé et de la Commission Nationale de l'Informatique et des Libertés (CNIL) et approuvée par le comité d'éthique de Paris-Boulogne et est conforme aux standards éthiques internationaux.

La cohorte a été constituée initialement pour évaluer l'incidence du syndrome métabolique sous antidépresseur.

2.2 POPULATION

2.2.1 Critère d'inclusion

Les sujets inclus dans l'étude sont âgés de 18 à 70 ans, et sont hospitalisés ou consultent dans les services de Psychiatrie suivants : CHU de Bicêtre, CHU Saint-Antoine, Hôpital Fernand Widal, CHU de Grenoble, CHU de Lille et CHU de Besançon. Ils présentent un EDC actuel dans le cadre d'un TDU selon les critères du DSM-IV-TR (APA 2000), attesté par l'entretien standardisé MINI (Mini International Neuropsychiatric Interview [51], avec une note totale d'au moins 18 à l'échelle de dépression de Hamilton (HAMD-17, Hamilton, 1967-Traduction française).

Ils nécessitent l'introduction d'un traitement antidépresseur (toutes molécules commercialisées) ou d'un traitement par Electroconvulsivothérapie (ECT).

Les patients donnent leur consentement libre et éclairé par écrit avant l'inclusion.

2.2.2 Critères d'exclusion

Les sujets présentant un trouble bipolaire (DSM-IV), un trouble psychotique actuel (DSM-IV), une dépendance à l'alcool, à l'héroïne ou aux psychostimulants (DSM-IV) ne sont pas inclus dans l'étude. Il en est de même pour les patients recevant un traitement par

thymorégulateur (sels de lithium, valproate de sodium, acide valproïque, valproate de sodium, carbamazépine) et les patients sous antipsychotiques.

Une symptomatologie psychiatrique d'origine organique, des pathologies médicales instables ou une grossesse en cours sont des critères de non-inclusion. Ils sont laissés à l'appréciation du clinicien. Les patients relevant d'une mesure d'hospitalisation sous contrainte d'une mesure de tutelle ou de curatelle ne peuvent être inclus.

2.3 TRAITEMENTS

2.3.1 Traitements évalués

Le traitement par antidépresseur est introduit de façon naturaliste, c'est-à-dire, en conditions réelles de prescription.

Tous les antidépresseurs commercialisés au moment de l'étude et prescrits aux posologies recommandées par l'AMM sont : les ISRS (fluoxétine (20 à 60 mg/j), paroxétine (20 à 50 mg/j), sertraline (50 à 200 mg/j), citalopram (20 à 60 mg/j), escitalopram (10 à 20 mg/j), fluvoxamine (100 à 300 mg/j)) ; les IRSNa (venlafaxine (75 à 350 mg/j), milnacipran (50 à 100 mg/j), duloxétine (60 à 120 mg/j)) ; les tricycliques (clomipramine (50 à 150 mg/j), amitryptiline (50 à 150 mg/j), imipramine : (50 à 150 mg/j)) ; les autres antidépresseurs (miansérine (30 à 90 mg/j), mirtazapine (15 à 45 mg/j), agomélatine (25 à 50 mg/j), tianeptine (25 à 37,5mg/j), iproniazide (50 à 100 mg/j), moclobémide (300 à 600 mg/j)).

Les traitements par ECT font également partie des traitements à l'étude.

Les patients qui changent de classe de traitement sont sortis de l'étude et peuvent être ré-inclus comme un nouveau patient. Ceci permet d'évaluer l'impact de la classe thérapeutique sur l'évolution de la symptomatologie dépressive.

2.3.2 Traitements tolérés

Les benzodiazépines sont tolérées. Elles sont prescrites à la dose minimale efficace. Les neuroleptiques (cyamémazine) et antihistaminiques H1 (hydroxyzine) à visée anxiolytique/hypnotique sont tolérés aux doses minimales efficaces et pour des durées aussi brèves que possible. Leur prescription ne doit pas excéder une durée de 14 jours.

2.4 RECUEIL DE DONNÉES

2.4.1 Données générales

Un psychiatre et un psychologue, lors d'un entretien et via les dossiers médicaux, recueillent, à l'inclusion, les informations sur :

- Les caractéristiques sociodémographiques
- Les antécédents médicaux
- L'hygiène de vie (tabac, alcool, etc.)
- Les caractéristiques cliniques

Les données sont recueillies à l'inclusion et lors du suivi après 1 mois (M1), 3 mois (M3) et 6 mois (M6) de traitement antidépresseur.

2.4.2 Données liées à la dépression

Un psychiatre et un psychologue, lors d'un entretien et via les dossiers médicaux, recueillent, à l'inclusion, les informations sur :

- Les tentatives de suicide (TS) récentes (datant de moins de 1 mois)
- Les TS anciennes (>1 mois)
- Les antécédents d'EDC (présence ou absence)
- Les antécédents de traitement antidépresseur (présence ou absence)
- Le traitement antidépresseur actuel

Ils évaluent la sévérité par hétéro-questionnaire (Echelle de Dépression de Hamilton 17 items (HAMD-17)) à l'inclusion et lors du suivi après 1 mois (M1), 3 mois (M3) et 6 mois (M6) de traitement antidépresseur.

2.4.3 Données génétiques

Les prélèvements sanguins sont réalisés lors de l'inclusion. L'ADN génomique est isolé à partir de sang total prélevé sur tubes EDTA. Le génotypage du polymorphisme du TRKB est réalisé au laboratoire de pharmacogénétique dans le département de pharmacologie

de la Faculté de Médecine de Paris Sud, sous la supervision du Dr Céline Verstuyft et du Pr Laurent Becquemont.

Les analyses génotypiques sont effectuées en aveugle des évaluations cliniques. Les résultats donnent 100 % de concordance entre le séquençage et le génotype déterminé par discrimination allélique. De même, il est observé 100 % de concordance entre les sujets évalués à 2 reprises.

2.5 STATISTIQUES

2.5.1 Données d'analyse

2.5.1.1 Caractéristiques cliniques de la dépression

Les caractéristiques cliniques de la dépression sont :

- La sévérité à l'inclusion (HAMD-17)
- Les tentatives de suicide (TS) récentes (datant de moins de 1 mois)
- Les TS anciennes (>1mois)
- La récurrence (présence ou absence d'EDC antérieur)
- Les antécédents de traitement antidépresseur (présence ou absence)

2.5.1.2 Réponse thérapeutique

La réponse thérapeutique après traitement par antidépresseur à M1, M3 et M6 est évaluée à partir de :

- Le score à l'échelle HAMD-17
- La réponse : amélioration de 50 % du score de l'échelle l'HAMD-17 [52]
- La rémission : obtention d'un score à l'échelle HAMD-17 inférieur ou égal à 7 [52]

2.5.1.3 Données génétiques

Notre étude s'est concentrée sur 8 SNP du TRKB (**Tableau 1**):

SNP	Position	fonction	A1	A2	Gene	Freq A1
rs1439050	87288192	intron	G	T	NTRK2	0,673
rs1187352	87293456	intron	A	G	NTRK2	0,358
rs1778933	87324410	intron	C	T	NTRK2	0,350
rs2289658	87563369	exon syn	A	G	NTRK2	0,960
rs2289657	87563459	intron	G	T	NTRK2	0,942
rs2289656	87563561	intron	C	T	NTRK2	0,832
rs3824519	87570003	intron	C	T	NTRK2	0,916
rs56142442	87636264	exon syn	C	T	NTRK2	0,949

Tableau 1 : Description des SNP étudiés et notation

Légendes : Position : sur le chromosome 9 ; A1/2 : allèle noté 1/2 dans notre notation et correspondance avec son nucléotide; syn : synonyme ; Feq : fréquence allélique dans la population selon base SNPdb (CEU : avec ancêtre de l'Europe du nord et de l'ouest)

rs1778933, rs1187352, rs3824519 et rs1439050 ont été sélectionnés à partir de l'étude de Perroud [53]. Ces SNP sont associés aux idées suicidaires chez des malades déprimés. Cependant, à notre connaissance, leur impact sur l'efficacité des antidépresseurs n'a jamais été évalué.

Les quatre autres SNP ont été choisis à partir de l'étude de Dong parmi ceux ayant potentiellement l'impact le plus marqué sur l'efficacité des antidépresseurs, ces 4 SNP perdant la significativité de leur impact après correction pour analyse d'un grand nombre de SNP [40].

Les fréquences attendues et observées des allèles dans chaque sous-groupe, selon le principe d'équilibre de Hardy-Weinberg, ont été comparées à l'aide d'un test de Chi-2. Le principe d'équilibre de Hardy-Weinberg est un modèle mathématique qui prédit la répartition des allèles dans une population illimitée sans mutation ni dérive génétique. Il est utilisé pour savoir si l'échantillon de personnes étudiées représente, au niveau génétique, la population générale.

Nous avons décrit initialement les SNP en 3 groupes (on notera pour simplifier les 3 génotypes de la sorte : 1 1 - 1 2 - 2 2) et en 2 groupes (en groupant le génotype hétérozygote avec l'un des deux génotypes homozygotes 1(11+12) vs 22 et 2(22+12) vs 11).

2.5.2 Tests statistiques

Le data-management et les analyses statistiques ont été réalisés sous la supervision du Dr Romain Colle et du Pr Emmanuelle Corruble à partir des logiciels Excel et R version 3.0.2.

La distribution de l'amélioration de l'échelle d'Hamilton (HAMD-17) a été étudiée en utilisant une appréciation graphique et des quantile-quantile plots. Les variables quantitatives sont décrites par des moyennes et écarts-types (e-t) et les variables qualitatives par des pourcentages.

Des analyses bivariées ont été réalisées : tests t de Student, tests F d'analyse de variance (ANOVA), tests U de Mann Whitney et H de Kruskal-Wallis pour les variables quantitatives et tests de Chi-2 pour les variables qualitatives. Des corrélations de Spearman ont été utilisées pour évaluer les liens entre 2 variables quantitatives. Des tests paramétriques ont été utilisés quand la distribution suivait une loi normale et que le nombre de sujets dans chacun des échantillons comparés était supérieur à 20, des tests non-paramétriques dans les autres cas.

Nous avons effectué des analyses multivariées à l'aide de régression linéaire pour les variables quantitatives et régression linéaire généralisée pour les variables qualitatives.

Le seuil de significativité statistique retenu est de 0.05. Cela correspond dans un modèle linéaire gaussien à un risque de 5 % de conclure à tort. Pour prendre en compte les analyses multiples et donc l'augmentation du risque d'avoir un lien significatif dû au hasard, nous avons appliqué une correction de Bonferroni. Cela consiste à diviser ce seuil par le nombre de tests effectués.

2.6 DESCRIPTION GENERALE DE LA COHORTE

624 patients avec un TDU, présentant un EDC actuel nécessitant l'introduction d'un traitement antidépresseur ont été inclus dans la cohorte. L'âge moyen est de 45,1 ans, 69.4 % sont de sexe féminin, 566 (90,7 %) sont caucasiens et 87.5 % sont hospitalisés.

Le score HAMD-17 moyen à l'entrée était de 24.7 avec un écart type de 5.0, 22.4 % avaient une TS récente, 45.8 % avaient une TS ancienne, 74.5 % avaient un antécédent d'EDC et 77.1 % avaient un antécédent de traitement antidépresseur, au moment de l'inclusion.

Les patients recevaient pour 38.9 % des ISRS (n=243), pour 38.3 % des IRSN (n=239), pour 8.8 % des tricycliques (n=55) et pour 8.8 % d'autres antidépresseurs incluant les IMAO (n=55).

Il y avait un taux d'attrition de 24.6 %, 47 % et 60.9 % respectivement au 1^{er}, 3^e et 6^e mois. La **figure 1** montre les motifs de sortie de l'étude.

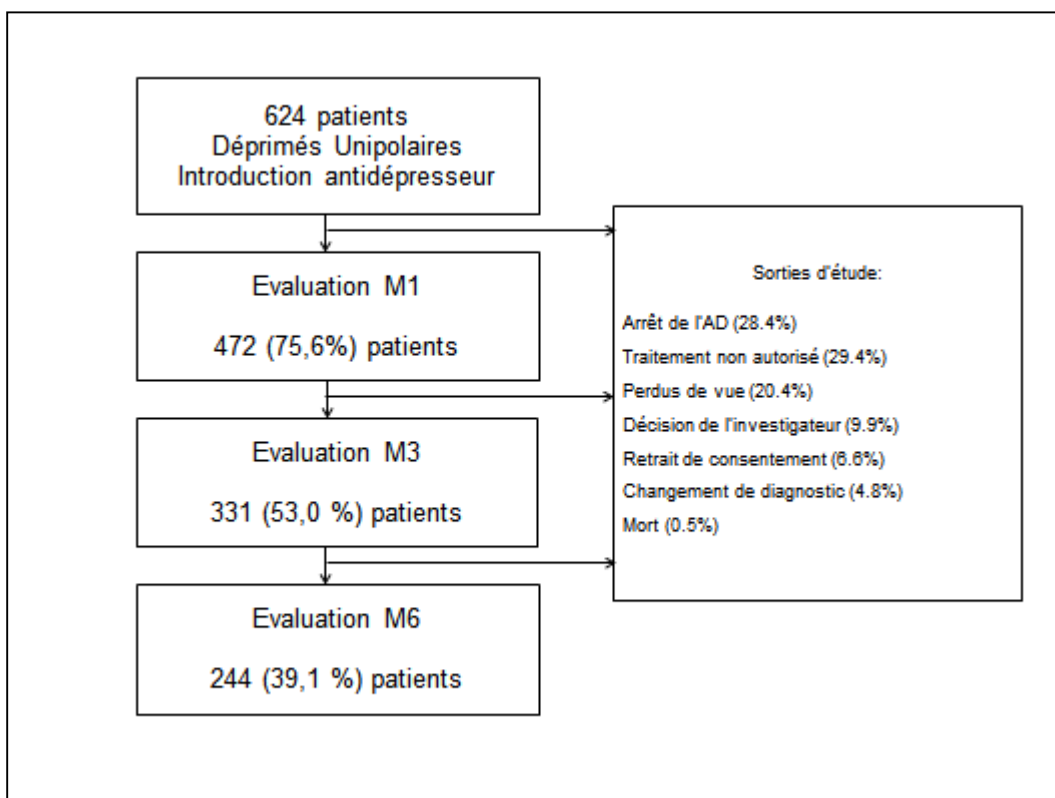


Figure 2 : Diagramme de flux de la cohorte METADAP

Légendes ; M1, M3 et M6 : au 1^{er}, 3^e et 6^e mois ; AD : antidépresseur

3 RESULTATS

3.1 ASSOCIATION ENTRE DES POLYMORPHISMES DU TRKB ET LES CARACTERISTIQUES CLINIQUES DE LA DEPRESSION

Cette première partie est consacrée à l'étude de l'influence des polymorphismes génétiques du TRKB sur les caractéristiques cliniques de la dépression BDNF/TRKB (**Figure 3**). Cette recherche a fait l'objet d'une publication dans Plos One. Le texte est présenté en anglais tel qu'il a été publié (à l'exception de la numérotation des tables et figures).

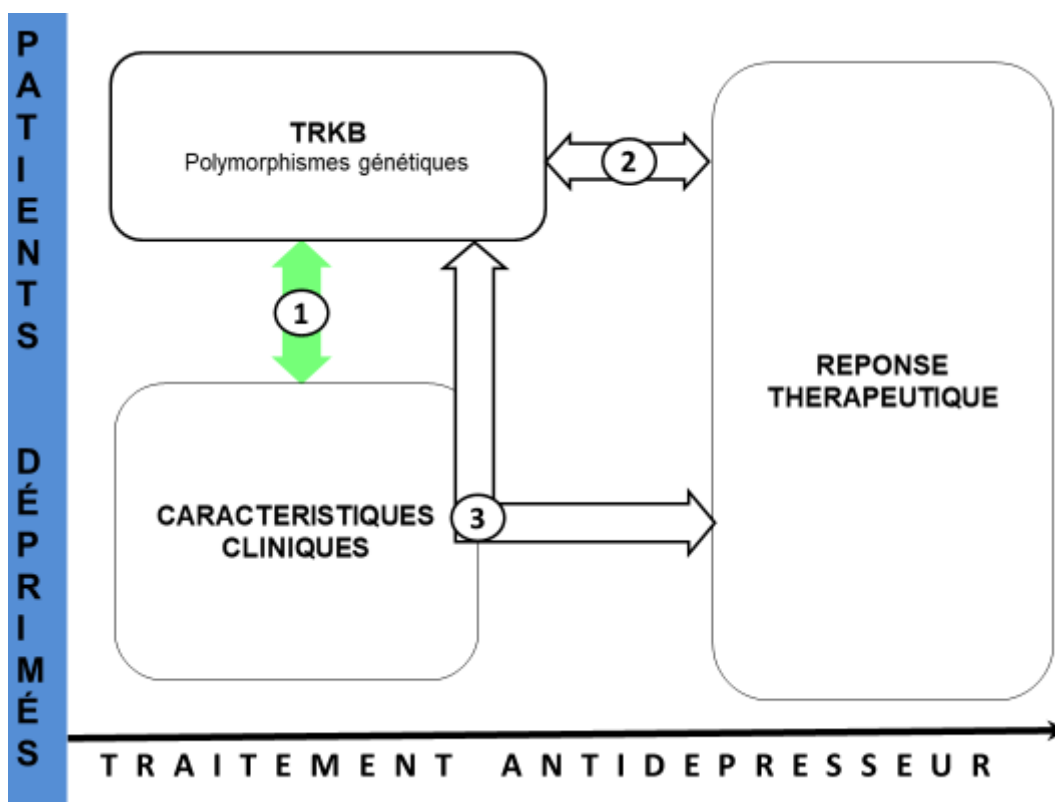


Figure 3 : Etape 1 de la thèse

Légendes ; TRKB : Récepteur Tyrosine-Kinase B

3.1.1 Article 1



RESEARCH ARTICLE

The TRKB rs2289656 genetic polymorphism is associated with acute suicide attempts in depressed patients: A transversal case control study

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Abstract

Introduction

Suicide Attempts (SA) are the main complications of Major Depressive Episodes (MDE) and are difficult to predict. Suicide is associated with the expression of Receptor Tyrosin-Kinase B (TRKB), the receptor of the Brain Derived Neurotrophic Factor (BDNF) involved in MDE. However, the impact of its genetic polymorphisms as predictive factors of SA should be clarified. Our main aim is to assess the association of 8 TRKB genetic polymorphisms and SA in depressed patients.

Material and methods

In 624 patients currently experiencing an MDE in the context of Major Depressive Disorder (MDD) (METADAP study), we assessed the association between 8 TRKB genetic polymorphisms (rs1778933, rs1187352, rs2289658, rs2289657, rs2289656, rs3824519, rs56142442 and rs1439050) and acute (previous month) or past (older than one month) SA. Bonferroni corrections and multivariate analysis adjusted for age, sex, level of education, marital status, Hamilton Depression Rating Scale score and previous MDE were used.

Results

The rs2289656 was associated with acute SA (CC = 28.5%, CT = 15.0% and TT = 11.5%, $p = 0.0008$). However, the other SNPs were not. Patients with the CC genotype had a higher

3.1.2 Abstract

INTRODUCTION

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RESULTS

The rs2289656 was associated with acute SA (CC = 28.5%, CT = 15.0% and TT = 11.5%, $p = 0.0008$). However, the other SNPs were not. Patients with the CC genotype had a higher rate of acute SA (28.5%) as compared to T carriers (14.6%) (adjusted OR = 2.2, CI95% [1.4; 3.5], $p < 0.0001$).

CONCLUSION

The TRKB rs2289656 CC genotype is associated with a 2.2 fold higher risk of acute SA in depressed patients. If this result could be confirmed, this TRKB SNP may be assessed to contribute to the prediction of SA in depressed patients.

3.1.3 Introduction

Suicide Attempts (SA) are the main complications of Major Depressive Episodes (MDE). 15% of patients with MDE attempt suicide during their life [54]. Their risk of SA and of suicide death is respectively about 20 fold (odds ratio [OR] = 7.8–29.9) [55] and 6 fold higher than the general population [56]. Major Depressive Disorder (MDD) is the leading cause of SA and suicide deaths (40% of SA and 60% of the suicide deaths) [57]. The prediction of SA during MDE is difficult for clinicians and is a major public health issue. Thus, it could be useful to identify biomarkers that could improve the prediction of SA. Genetic biomarkers are of interest since heritability of suicidal behavior is high [58]. So, the purpose of this study is to identify genetic biomarkers of SA in depressed patients that may contribute to prevent SA in depressed patients.

The Tyrosine Kinase Receptor B (TRKB), which is the main receptor of the Brain Derived Neurotrophic Factor (BDNF), activates neuronal survival, plasticity, neurogenesis and synaptic connectivity [26]. BDNF is associated with major depressive episodes [59]. Interestingly, the BDNF/TRKB pathway and suicide may be linked. Indeed, TRKB and BDNF protein expression are decreased in the prefrontal cortex and hippocampus of suicide completers as compared to non-psychiatric healthy controls [60]. And an association between the BDNF Val66Met genetic polymorphism and SA was identified in a sample of 170 Italian depressed patients [61]. There were a lot of data involving BDNF and its main receptor TRKB in the neurobiology of suicide [62]. In depressed patients, most of the genetic studies regarding suicide attempts dealt with BDNF, whereas TRKB has been poorly explored [63].

Two recent post-mortem studies have investigated TRKB genetic polymorphisms in suicidal completers. The study performed by Ropret and colleagues did not find any association between 5 TRKB SNPs and suicide [64]. However, another one reported that 2 out of 17 TRKB SNPs (rs10868235 and rs1867283) were associated with suicide [65].

To the best of our knowledge, out of 4 studies comparing TRKB genetic polymorphisms in MDE patients with or without lifetime SA [66-69]. 3 were negative. In the Schosser et al. study [69], comparing depressed cases and controls in a European cohort of 2023 patients, there was no association between TRKB SNPs and suicidal behavior. Similarly, no association between TRKB SNPs and lifetime suicide attempts was shown in the Perlis' study [68] in the STAR * D American cohort of 1273 MDD and 3117 bipolar patients, and in the Mullins' study [67] in a European cohort of 3270 bipolar and MDD patients. Only one study identified five TRKB SNPs out of 69 (rs10868235, rs1147198, rs1867283, rs1187286,

and rs11140800) in German depressed patients [70]. This study found that there was a significant association with lifetime SA for these SNPs in two independent samples (a primary sample (n = 394) and a replication sample (n = 744)). Another case-control study in 159 psychiatric patients (all diagnoses included) reported a significant association between the TRKB rs1659400 SNP and lifetime SA in 71 females but not in males [71]. Four genetic studies have focused on suicidal ideation under antidepressant drug treatment. Voegeli et al. (2016) [72], in a case-control cohort of 3771 French depressed patients found a significant association between antidepressant-associated worsening of suicidal ideation and the rs1439050 but not 12 other TRKB SNPs. Perroud et al., 2009 [73], in a cohort of 811 European antidepressant-treated depressed patients reported an association between 4 TRKB SNPs (rs1187352, rs1778933, rs3824519, rs1439050) and antidepressant-associated worsening of suicidal ideation, that do not stand after correction for multiple comparisons. In the two other genome-wide association studies (GWAS), in two cohorts of 1953 European depressed patients treated with selective serotonin reuptake inhibitors (SSRI) and 706 European antidepressant-treated depressed patients, there was no evidence for an association between TRKB SNPs and antidepressant-associated worsening of suicidal ideation [74,75]. However, there are some inconsistencies that may be due to limits in the methodology related to study designs. Some of them [66-69] studied lifetime SA, assessed retrospectively through patient interviews. This methodology has two limits, first the memory bias related to delay between SA and assessment, and second the declarative bias of SA which are under-declared by patients [76-79]. Indeed, more than one third of patients with major depression misreport their history of SA [77]. Other studies [72], [73] assessed suicidality prospectively using specific items of depression scales. But, in these studies, SA were not assessed and there was a discrepancy between individuals with suicide ideation and suicide attempters [80]. To overcome these limits, we proposed to study SA and more specifically acute SA in MDE patients with both self-assessment and assessments by professionals of mental health. Furthermore, 8 TRKB SNPs (rs1778933, rs1187352, rs2289658, rs2289657, rs2289656, rs3824519, rs56142442 and rs1439050) were not previously or poorly explored and were potentially relevant.

Our primary objective was to compare 8 TRKB SNPs genotypes (rs1778933, rs1187352, rs2289658, rs2289657, rs2289656, rs3824519, rs56142442 and rs1439050) in patients with and without acute SA. Then, our secondary objective was to compare TRKB SNPs genotypes in patients with and without past SA.

3.1.4 Material and Methods

Designs

This was a transversal case-control study, using the METADAP study [50], registered by the French National Agency for Medicine and Health Products Safety (ANSM) and the Commission Nationale de l'Informatique et des Libertés (CNIL), approved by the Ethics Committee of Paris-Boulogne, France, and conforming to international ethical standards. The association between 8 TRKB SNPs and suicide attempts were assessed in patients with a current MDE.

Patients

Since suicidal behaviors may be multifactorial, we focused on a homogenous sample of patients with a current major depressive episode in a context of MDD. Patients were aged 18–65 years, with a current MDE diagnosis in a context of Major Depressive Disorder (MDD) (DSM-IVTR) based on the Mini International Neuropsychiatric Interview (MINI), with a minimum depression score of 18 on the 17-item Hamilton Depression Rating Scale (HAM-D) [81]. Patients with DSM-IVTR bipolar disorders, psychotic disorders, current substance abuse or dependence, pregnancy, breast feeding, organic brain syndromes or unstable medical conditions were excluded. Patients were provided written informed consent for study participation and for genetic analyses. Clinical assessments were performed blind to genotyping results.

Suicide attempts

The main criterion was acute SA, defined by a self-destructive act with some intent to end one's life which occurred in the month before the assessment [82]. Acute SA were assessed firstly through patient interviews with both a psychiatrist and a psychologist, and secondly were screened in the medical records. This strategy using both self-assessment and assessment by others was chosen to overcome memory bias and declarative bias. The secondary criterion was past SA, defined as those occurring more than one month before assessment. Past SA were assessed by patient interviews with both a psychiatrist and a psychologist. Past SA were chosen as secondary criteria because they suffer particularly from memory and declarative biases.

Genotype

We focused on SNPs which were not previously or poorly explored and that were potentially relevant. 5 SNPs (rs1778933, rs1187352, rs3824519, rs1439050 and, rs2289656) were identified for their potential association with suicidality in previous studies [72], [73], [66].

One of those SNP (rs2289656) was associated with Alzheimer disease [83]. We also assessed three SNPs never assessed with SA (rs2289658, rs2289657, rs56142442), because the Dong's study showed that they have a possible impact on the efficacy of antidepressant in patients with MDD [40]. Six of them were introns and the two others were synonymous exons (**Table S1**).

Genomic DNA was extracted from circulating blood leucocytes by using Gentra Puregene Blood Kits according to the manufacturer's protocol (Qiagen) and was stored at -20°C.

The TRKB polymorphisms were genotyped by the IntegraGen company (Evry, France) using TaqMan allelic discrimination [84] ([dx.doi.org/10.17504/protocols.io.ti2ekge](https://doi.org/10.17504/protocols.io.ti2ekge)).

Statistical analysis

The statistical analysis was performed with the R 3.2.2 software. Linkage disequilibrium (LD) between the 8 SNPs was assessed using THESIAS 3.1 software [85]. After testing the Hardy-Weinberg equilibrium using Chi 2 tests, each SNP was studied in 3 groups (two homozygote and one heterozygote groups). Regarding SNP with a significant association in 3 groups, we performed a complementary analysis in two groups (the heterozygote group being associated with one of the homozygote groups to test dominant and recessive models). We performed a complementary allelic analysis.

Due to the number of SNPs studied and to take into account the increased risk of false positive results due to the high number of comparisons, Bonferroni's corrections were applied, the threshold for significance being $0.05/8 = 0.00625$.

We performed bivariate analyses to assess associations between TRKB SNPs genotypes (and alleles) and socio-demographic clinical variables. Then, for the primary and secondary objectives, inter-genotypic comparisons were computed using Chi2 for acute SA and past SA. Logistic regressions were performed to control for potential confounders among demographic and clinical variables. Indeed, covariables of the multivariate models were selected on the basis of a significant association ($p < 0.05$) in bivariate analyses with acute SA, past SA or SNPs. Adjustments were performed on age, sex, level of education, marital status, HAMD score, previous antidepressant treatment and previous MDE.

Due to the heterogeneity of the sample, the previous analysis was performed first in the whole sample and second in the Caucasian (patient with 2 Caucasian parents) subgroup of patients.

3.1.5 Results

Sample characteristics

Among the 624 depressed patients of the METADAP study, only 569 patients had a DNA sample. They were mainly women (69.6%). Their mean age was 46.2 years (sd = 13.2). Their mean HAMD score at baseline was 24.6 (sd = 5.0). Five hundred and twenty-one (92%) patients were Caucasian.

Suicide attempts

22.8% of patients had an acute SA. 50.8% of patients with acute SA had a past SA. Socio-demographical and clinical characteristics of these patients are shown in **Table S2**. Patients with acute SA were younger, had higher HAMD scores as compared to patients without acute SA. There was no significant difference in the other demographic and clinical features. Patients with past SA had a higher frequency of recurrent MDE and previous antidepressant drug treatment. There was no significant difference in the other demographic and clinical features.

TRKB genetic polymorphisms

Table S3 showed the allelic repartition of the eight TRKB SNPs. Since there were no homozygous patients for the minor allele and only three heterozygous patients for the rs56142442, this SNP was not analyzed. There was a deviation from the Hardy–Weinberg equilibrium for two other SNPs (rs2289658 and rs3824519). The haplotype analysis (**Table S4**) showed that rs1439050, rs1187352 and rs1778933 were in moderate linkage disequilibrium and that rs2289658, rs2289657, rs2289656 and rs3824519 were in high linkage disequilibrium.

There was no significant difference between the 8 TRKB genetic polymorphisms in the demographic and clinical features after Bonferroni correction (in the 3 group analysis and in the complementary 2 group analysis) except for educational level ($p = 0.001$ with rs1439050, $p = 0.003$ with rs1187352). The demographic and clinical features of the cohort according to each SNP are described in **Table 2**. The genotype groups did not significantly differ for these demographic and clinical features after Bonferroni corrections except educational level for rs1439050 and rs1187352.

TRKB genetic polymorphisms and suicide attempts

There was an association between the rs2289656 and acute SA (bivariate: $p = 0.0008$ and adjusted: $p = 0.003$) (**Table 2**). The rs2289656 CC genotype, the major homozygote allele, was associated with higher rates of acute SA, as compared to CT (OR = 2.3, CI95% [1.4–3.7], adjusted OR = 2.1, CI95% [1.3–3.5]) and TT genotypes (OR = 3.1, CI95% [1.03–13.1], adjusted OR = 3, CI95% [1–12.9]). There was no association between rs2289656 and past SA. No significant association was observed with the 7 other SNPs.

In the 2-group analysis, a stronger association between rs2289656 and acute SA was observed (adjusted $p = 0.001$). Indeed, patients with the CC genotype had a higher rate of acute SA (28.5%) as compared to T carriers (14.6%) (OR = 2.3, CI95% [1.5; 3.7], adjusted OR = 2.2, CI95% [1.4–3.5]) (**Figure 4**). There was no association between rs2289656 and past SA. There was no significant association for the other SNPs.

The allelic analysis confirmed the association between rs2289656 and acute SA (bivariate: $p = 0.0002$; adjusted: $p = 0.001$). Indeed, patients with the C allele had a higher rate of acute SA (25.7%) than T carriers (14.2%) (OR = 2.1, CI95% [1.4–3.2], adjusted OR = 2.0, CI95% [1.3–3.0]) (**Table S5**). There was no association between SNPs and past SA. There was no significant association for the other SNPs.

	rs1439050			rs1187352			rs1778933			rs2289658			rs2289657			rs2289656			rs3824519		
Genotype	GG	GT	TT	GG	GA	AA	TT	TC	CC	AA	AG	GG	GG	GT	TT	CC	CT	TT	CC	CT	TT
Patients (n)	194	265	73	266	223	59	280	215	56	504	39	4	514	37	2	340	181	26	468	75	9
Caucasian patients (n)	190	236	60	243	204	56	252	196	55	467	31	2	475	29	2	307	169	25	432	65	8
Age (m(sd))	45 (13.3)	46.5 (13.1)	49 (13.0)	45.7 (12.8)	46.4 (13.6)	47.9 (12.6)	45.7 (12.7)	47.4 (13.5)	44.7 (13)	46.2 (13.3)	45.6 (11.3)	58.1 (1.7)	46.2 (13.2)	47.3 (11.2)	59.5 (0.3)	45.1 ^a (13.6)	48.3 ^a (12.0)	47.9 ^a (12.2)	46.4 (13.3)	45.3 (11.5)	47.2 (14.2)
Women (%(n))	71.6 (139)	69.4 (184)	68.5 (50)	69.9 (186)	71.7 (160)	64.4 (38)	68.6 (192)	72.6 (156)	69.6 (39)	71.4 (360)	59 (23)	50 (2)	70.6 (363)	62.2 (23)	0 (0)	69.7 (237)	69.1 (125)	84.6 (22)	70.3 (329)	68 (51)	55.6 (5)
Single (%(n))	51.5 (100)	51.3 (136)	60.3 (44)	56.4 (150)	48.4 (108)	57.6 (34)	51.1 (143)	51.6 (111)	66.1 (37)	52.2 ^b (263)	64.1 ^d (25)	0 ^a (0)	52.7 (271)	56.8 (21)	0 (0)	57.1 (194)	44.8 (81)	53.8 (14)	52.4 (245)	57.3 (43)	22.2 (2)
High educational level (%(n))	53.1 ^a (103)	36.2 ^a (96)	47.9 ^a (35)	61 ^b (125)	37.7 ^b (84)	47 ^b (36)	57.1 ^c (129)	39.1 ^c (84)	46.1 ^c (32)	44.2 (223)	53.8 (21)	0 (0)	44.4 (228)	51.4 (19)	0 (0)	47.9 (163)	39.8 (72)	30.8 (8)	43.8 (205)	49.3 (37)	11.1 (1)
Smoking (%(n))	41.8 (81)	34.7 (92)	32.9 (24)	40.7 (111)	30 (67)	41.7 (24)	39.3 (108)	33 (71)	38.6 (22)	36.1 (182)	43.6 (17)	0 (0)	36.2 (186)	45.9 (17)	0 (0)	35 (119)	35.9 (65)	61.5 (16)	35.7 (167)	45.3 (34)	33.3 (3)
Recurrent MDD (%(n))	76.2 (147)	74 (196)	75.3 (55)	73.6 (195)	75.3 (168)	81.4 (48)	71.7 (200)	78.1 (168)	78.6 (44)	75.5 (380)	74.4 (29)	50 (2)	75 (385)	73 (27)	100 (2)	77.1 (262)	70 (126)	84.6 (22)	74.7 (349)	76 (57)	77.8 (7)
HAMD-17 (m(sd))	24.2 (5.0)	24.6 (4.7)	24.9 (5.3)	24.3 (4.8)	24.7 (5.0)	25 (4.8)	24.6 (5.0)	24.3 (4.8)	25 (4.9)	24.5 (4.9)	25.1 (5.5)	23 (3.6)	24.5 (4.9)	24.7 (5.7)	26 (1.4)	24.5 (5.1)	24.4 (4.8)	24.8 (3.3)	24.5 (4.8)	24.2 (5.7)	25.8 (3.6)
antidepressant drug free (%(n))	41,2 (80)	34,3 (91)	38,4 (28)	39,5 (105)	32,7 (73)	42,4 (25)	40 (112)	31,6 (68)	44,6 (25)	36,9 (186)	41 (16)	25 (1)	37,4 (192)	32,4 (12)	50 (1)	39,1 (133)	34,3 (62)	30,8 (8)	37,2 (174)	34,7 (26)	44,4 (4)
Previous antidepressant treatment (%(n))	77.7 (150)	79.6 (211)	76.7 (56)	74.7 (198)	83.4 (186)	78 (46)	74.6 (208)	84.2 (181)	76.8 (43)	79.1 (398)	71.8 (28)	100 (4)	78.6 (403)	78.4 (29)	100 (2)	77.1 (262)	80 (144)	88.5 (23)	78.6 (367)	80 (60)	77.8 (7)
Suicide Attempt																					
Past SA (%(n))	30.4 (59)	32.5 (86)	30.1 (22)	32 (85)	28.7 (64)	40.7 (24)	29.3 (82)	32.6 (70)	41.1 (23)	31.9 (161)	30.8 (12)	50 (2)	31.9 (164)	29.7 (11)	100 (2)	33.2 (113)	29.8 (54)	26.9 (7)	30.8 (144)	36 (27)	44.4 (4)
Acute SA (%(n))	23.3 (45)	20.4 (54)	28.8 (21)	27.1 (59)	23.3 (52)	22.3 (16)	26.8 (66)	21.9 (47)	23.7 (15)	23.1 (116)	25.6 (10)	0 (0)	23.4 (120)	21.6 (8)	0 (0)	28.5 (97)	15 (27)	11.5 (3)	22.7 (106)	24 (18)	22.2 (2)

Table 2 : Demographic and clinical features according to the TRKB genetic polymorphisms studied.

n: number of patient; *m*: mean; *sd*: standard deviation; *HAMD-17*: Hamilton Depression Rating Scale 17 items; *antidepressant drug free*: absence of antidepressant during 3 years before the inclusion; *previous antidepressant treatment*: past history of antidepressant treatment; *ant drug free in the 3 year before inclusion*; *MDD*: Major Depressive Disorder; *SA*: Suicide Attempt; *Past SA*: Suicide attempts were defined as those which occurred more than one month before assessment.

^a: *p*=0.001 (bivariate analysis) for inter-genotypic comparisons (3 groups); ^b: *p*=0.003 (bivariate analysis) for inter-genotypic comparisons (3 groups); ^c: *p*=0.039 (bivariate analysis) for inter-genotypic comparisons (3 groups); ^d: *p*=0.027 (bivariate analysis) for inter-genotypic comparisons (3 groups); ^e: age (*p*=0.025 (bivariate analysis) for inter-genotypic comparisons (3 groups); ^f: *p*=0.038 (bivariate analysis) for inter-genotypic comparisons (3 groups).

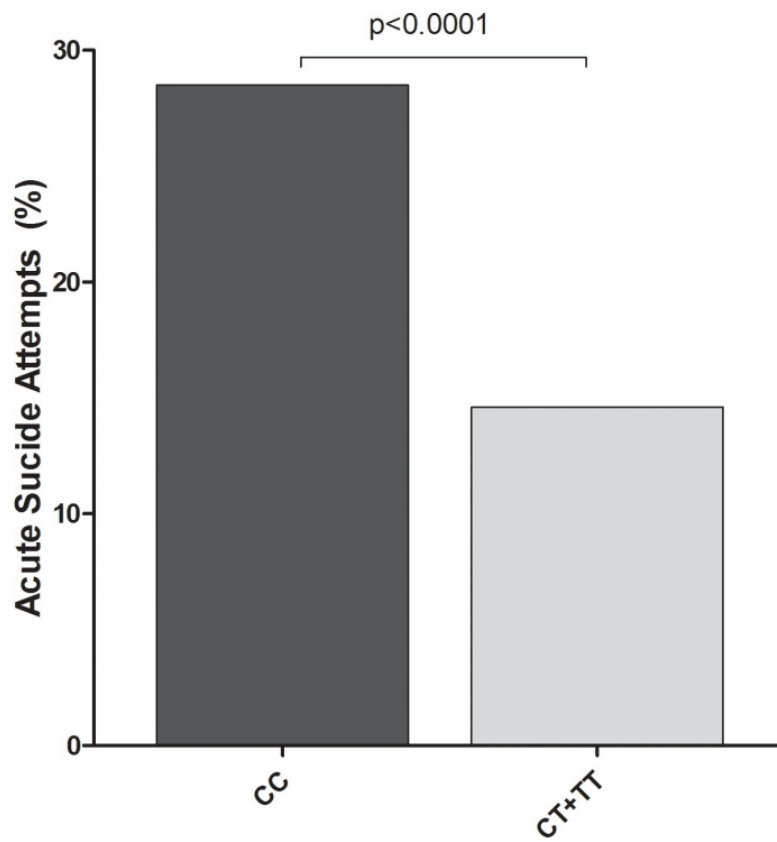


Figure 4 : Association between the TRKB rs2289656 and acute suicide attempts.

CC homozygotes versus (CT heterozygotes and TT homozygotes), p: bivariate p values.

TRKB genotype and suicide attempts in Caucasian patients

Similar results were found in the Caucasian subgroup (n = 521) with an association between the rs2289656 and acute SA (bivariate: $p = 0.002$ and adjusted $p = 0.005$). The CC genotype of the rs2289656 was associated with higher acute SA rates (CC: 29%, CT: 16.1%, TT: 12%) as compared respectively to CT (OR = 2.1, CI95% [1.3–3.5], adjusted OR = 2.1, CI95% [1.3–3.5]) and TT (OR = 3.0, CI95% [1.0–12.9], adjusted OR = 3, CI95% [1–13]) genotypes. There was no association between rs2289656 and past SA. No significant association was observed for the other 7 SNPs.

In the 2-group analysis, there was a stronger association between the rs2289656 and acute SA (bivariate: $p = 0.00059$, adjusted: $p = 0.002$). Patients with the CC genotype had a higher risk of acute SA as compared to T carriers (29% vs 14.6%, OR = 2.2 (CI95% [1.3; 3.6], adjusted OR = 2.1, CI95% [1.3–3.4]). There was no association between rs2289656 and past SA. There was no association for the other SNPs.

The allelic analysis confirmed the association between rs2289656 and acute SA (bivariate: $p = 0.0007$; adjusted: $p = 0.002$). Indeed, the C allele carriers had a higher rate of acute SA (26.2%) than the T allele carriers (15.1%) (OR = 2.0, CI95% [1.3–3.0], adjusted OR = 1.9, CI95% [1.3–2.9]). There was no association between rs2289656 and past SA and there was no significant association for the other SNPs.

Haplotype

The haplotype rs2289658, rs2289657, rs2289656 and rs3824519 with high linkage disequilibrium, were associated with acute SA. Patients with the AGCC genotype had a higher rate of acute SA than AGTC genotype carriers (OR = 2.2 (CI95% [1.4; 3.2]), $p = 0.00018$).

3.1.6 Discussion

The present study showed an association between the rs2289656 TRKB genetic polymorphism and acute SA in depressed patients. Indeed, patients with the CC genotype had 2.3 fold higher risk of acute SA as compared to T allele carriers. This SNP was not associated with MDD clinical features and remained significantly associated with acute SA after adjustment on MDD clinical and socio-demographical characteristics. Interestingly, in

Kohli's study [66], rs2289656 was not in linkage disequilibrium with the five TRKB SNPs significantly associated with lifetime SA. The rs2289656 was associated with Alzheimer disease (CC genotype is 3-fold more frequent in sporadic Alzheimer's disease than the CT genotype) [83]. Some studies show an association between suicide attempts and the neurogenesis pathway genes such as BDNF, of which TRKB is the main receptor [63]. The neurotrophin genes (BDNF, NGF and TRKB) have the strongest evidence for a role in SA [86]. As depression is associated with neurotrophins [87], it could potentiate the effect of genetics on suicide attempts. A previous study [66] found a trend ($p = 0.11$) between this rs2289656 and lifetime SA in a German MDD sample ($n = 394$). Here, we show a significant association between this SNP and acute SA in a larger French MDD-MDE cohort. There were previous published GWAS of suicide attempts that did not catch TRKB SNPs [63,67-69,86-88]. Considering the large number of SNPs studied, in order to have sufficient statistical power, at least ten thousands patients should have been included [89]. Actually, these previous GWAS on SA did not have this sample size.

There were two published GWAS of lifetime SA in non MDD patients. They included bipolar patients ($n = 5815$ and $n = 2698$) [68,90] and they did not catch any associations between TRKB SNPs and lifetime SA. Thus, it could be suggested that the association between TRKB rs2289656 and acute SA observed in our study could be specific of MDE patients. However, regarding the very high number of tested SNPs (2 millions in the first one and 724 0000 in the second one), these two GWAS may have lacked power to conclude to the absence of association between rs2289656 and lifetime SA in bipolar disorder.

The rs1439050 was associated with antidepressant-worsening suicidal ideation in two studies [72], [73]. In our study, in line with the replication cohort of Kohli [66], we failed to provide evidence for an association with acute SA. The discrepancy between Perroud or Voegeli and our results could be explained by the discrepancy between the main variable studied: suicidal ideation [72], [73] and suicide attempt in our study. Indeed, most patients with suicide ideation do not make suicide attempts [80]. The rs1778933, rs1187352, rs3824519 were associated with antidepressant-associated worsening of suicidal ideation but not after Bonferroni correction in the study of Perroud et al., [73]. Here, no association between these SNPs and acute SA was observed.

This study had some limits. Firstly, the rs2289656 was an intron and its biological effect remains unknown. Some introns have a role in the mechanism of splicing and can change the mRNA transcript or its amount [91] and are involved in several human diseases [92]. Interestingly, a study reported that introns had an impact on TRKB splicing [93].

Because no control group without MDE was available, we were not able to assess the specific effect of MDE on the association between TRKB rs2289656 and acute SA. We cannot exclude masking effects of MDE. And the generalizability of the association between TRKB rs2289656 and acute SA cannot be proposed for other mental disorders or for the general population. However, as MDE is the leading cause of SA [57], our results are particularly relevant in this subpopulation. No association between the rs2289656 and past SA was observed. This suggests that past SA assessment may suffer from biases related to the delay between past SA and assessment, and the under-declared past SA by patients [76-79]. These biases are inherent to retrospective assessments of past events. We decided to limit the number of SNPs to avoid false positives and focus on potentially relevant and poorly explored SNPs. So, in this study, we did not include the five Kohli's SNPs [66]. Finally, the effect size of rs2289656 impact is moderate (relative change 48.8%) and could partially predict acute SA in depressed patients. So, considered individually, the rs2289656 alone is not sufficient to predict acute SA but may contribute to this prediction. The total number of SA was not available in this study, because of the poor quality of such retrospective data collection in depressed patients because of cognitive symptoms. So, the associations between TRKB SNPs and total number of SA were not assessed. This study needs to be replicated in an independent cohort of MDE patients before introducing this biomarker in clinical assessments that could improve the accuracy of acute SA prediction.

This study has strengths. The sample size was large. The sample was well characterized and homogenous in terms of diagnosis (MDD patients with a current MDE only), with a majority of Caucasian patients. Furthermore, acute SA is a strong criterion: it is assessed by auto-evaluation, and evaluation by others, and medical records.

The BDNF/TRKB pathway has an influence on suicidality. There are epigenetic changes of BDNF and TRKB receptors in the brain of suicide patients [94] and Sarchiapone et al found an association between BDNF genetic polymorphisms and SA [61]. Although the functional and neurobiological significance of TRKB rs2289656 is poorly known, it has been shown to be associated with Alzheimer disease progression [83] suggesting that this SNP could be relevant. Since it is an intronic genetic polymorphism, it could play a role on alternative splicing. But further research is needed to understand the neurobiological significance of TRKB rs2289656 genetic polymorphism. To explore the generalizability of the association between TRKB rs2289656 and acute SA, future studies are needed in samples without MDE. These results need to be confirmed in future studies.

3.1.7 Conclusion

This study in depressed patients showed an association between the rs2289656 TRKB SNP and acute SA. If it could be confirmed, there could be a benefit to genotype this TRKB SNP in daily practice to predict SA in depressed patients.

3.2 REPONSE AUX ANTIDEPRESSEURS

Cette partie est consacrée à l'influence des polymorphismes génétiques du TRKB sur la réponse thérapeutique après traitements antidépresseurs chez des patients avec un EDC. L'influence des polymorphismes génétiques du TRKB est considérée isolément puis en intégrant les caractéristiques cliniques du TDU dans l'analyse.

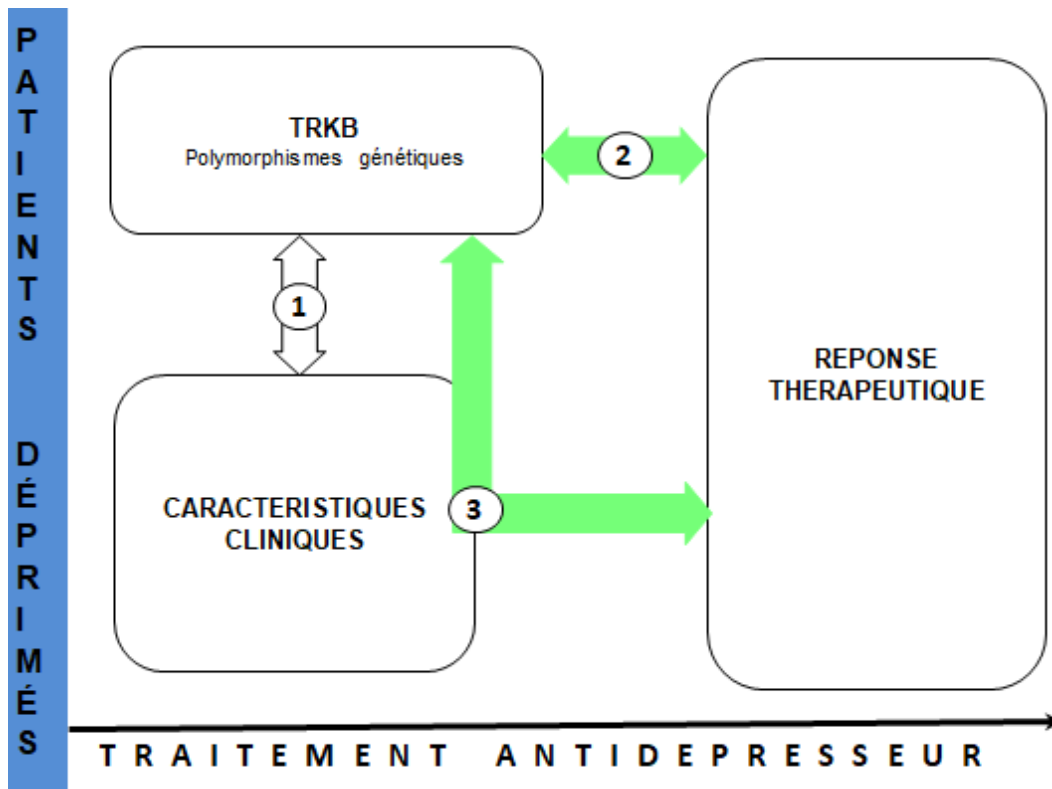


Figure 5 : Etape 2 et 3 de la thèse

Légendes ; TRKB : Récepteur Tyrosine-Kinase B

3.3 ASSOCIATION ENTRE DES POLYMORPHISMES DU TRKB ET LA RÉPONSE APRÈS TRAITEMENT ANTIDÉPRESSEUR

Cette partie s'est concentrée sur l'impact du polymorphisme génétique du TRKB sur la réponse/rémission sous antidépresseurs. Elle a fait l'objet de 2 articles dans *Pharmacogenomics*, une revue de la littérature et l'étude de 8 polymorphismes génétiques du TRKB sur la réponse/rémission sous antidépresseurs dans la cohorte METADAP.

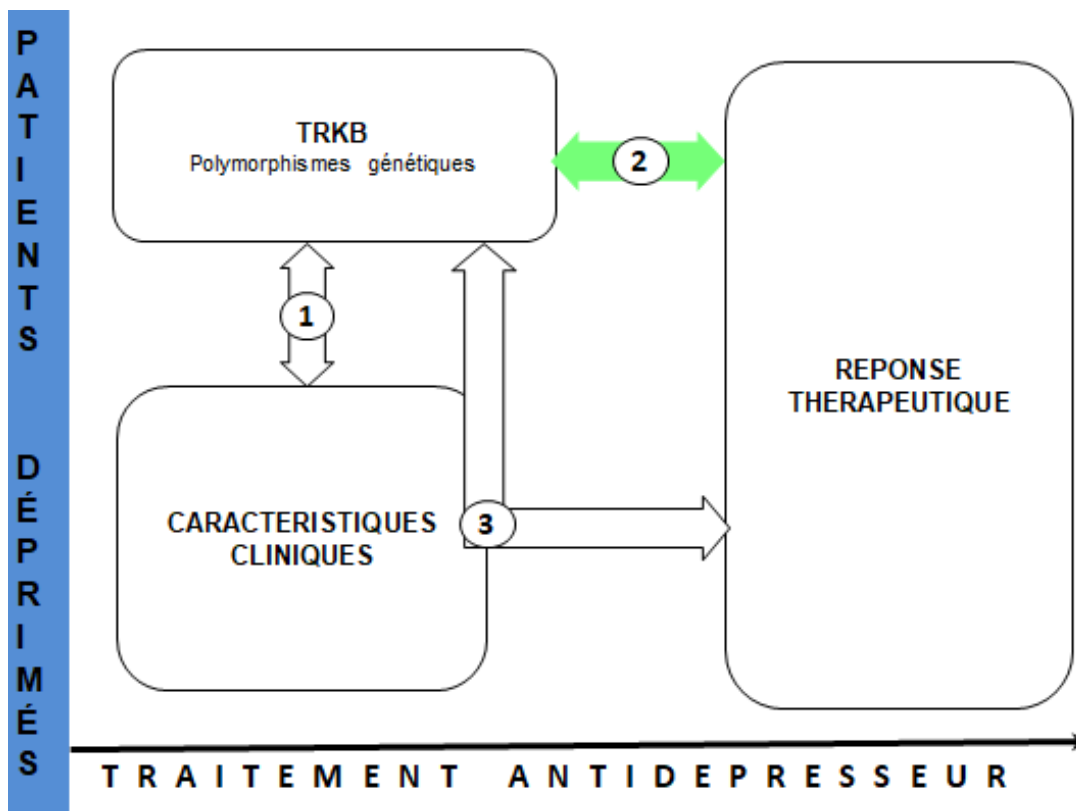


Figure 6 : Etape 2 de la thèse

Légendes ; TRKB : Récepteur Tyrosine-Kinase B

3.3.1 Article 2

Nous présentons une revue systématique et exhaustive concernant l'impact sur la réponse/rémission sous antidépresseurs des polymorphismes génétiques du BDNF et de ses récepteurs TRKB et PNTR75 dirigée par le Dr COLLE et le Pr CORRUBLE. Mon travail s'est concentré sur le TRKB. Ce travail a été publié dans la revue Pharmacogenomics [95], le texte est présenté en anglais tel qu'il est publié.

Review
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BDNF/TRKB/P75NTR polymorphisms and their consequences on antidepressant efficacy in depressed patients

We propose an extensive review of the literature about *BDNF/TRKB/P75NTR* polymorphisms and their consequences on antidepressant efficacy in depressed patients. Five genome-wide association studies and 30 association studies were included. Twenty seven studies focused on the Val66Met polymorphism (rs6265), the Met allele being associated with a higher antidepressant efficacy only in Asian patients. Other *BDNF/TRKB/P75NTR* polymorphisms (*BDNF*: rs7103411, rs7124442, rs908867, rs2049046, rs61888800, rs10501087, rs1491850; *TRKB*: rs10868223, rs11140778, rs1565445, rs1659412; *P75NTR*: rs2072446) were reported to be associated with antidepressant efficacy but these results were not replicated. Finally, there are 15 positive studies among 30 studies regarding *BDNF/TRKB/P75NTR* polymorphisms. The only SNP which benefits of at least three positive studies is the *BDNF* Val66Met polymorphism (rs6265). Consequently, with a lack of good and consistent studies, the clinical utility of *BDNF* in treatment selection is far from clear. We propose several recommendations for further studies.

Keywords: antidepressant remission • antidepressant response • BDNF • major depressive disorder • major depressive episode • PNTR75 • single nucleotide polymorphism • TRKB

Only a third of patients with major depressive episodes (MDE) achieve remission after 3 months of antidepressant treatment [1]. To reduce risks, suffering and minimize costs associated with major depressive disorder (MDD), it is useful to determine criteria that may predict antidepressant efficacy. To the best of our knowledge, these criteria are scarce [2]. Thus, the prediction of response and remission in depressed patients treated with antidepressant drugs remains a challenge for clinicians.

Growing evidence suggests the implication of adult brain plasticity, especially adult hippocampal neurogenesis in antidepressant efficacy [3–6], especially pharmacogenetic studies focusing on the brain-derived neurotrophic factor (BDNF) and its receptors tyrosine kinase receptor B (TRKB) and p75 neurotrophin receptor (P75NTR) (alternatively named as NGFR or tumor necrosis factor superfamily member 16, TNFRSF16).

The BDNF is a member of the neurotrophin family [7]. The *BDNF* gene comprises 11 exons that span about 70 kb of chromosome 11 [8]. BDNF, initially synthesized as 32 kD precursor protein called pro-BDNF, is intra- and extracellularly cleaved to produce the mature BDNF form [9,10]. Mature BDNF binds to TRKB receptors with high affinity [11,12]. The BDNF/TRKB couple increases neuronal plasticity, such as neurogenesis, neurite arborization and synaptogenesis. ProBDNF/P75NTR couple lead to programmed neuronal death, neurite retraction and synaptic pruning [12].

TRKB is mainly present in the central and peripheral nervous system [13,14]. This receptor is located on the cellular membrane and mediates the effects of BDNF through its extra- and intracellular domains. It is coded by a 24-exon gene that spans about 24 kb located on chromosome 9(q22.1) [15,16]. The binding of the BDNF dimer to TRKB induces dimer-



Pharmacogenomics

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3.3.2 Abstract

We propose an extensive review of the literature about BDNF/TRKB/P75NTR polymorphisms and their consequences on antidepressant efficacy in depressed patients. 5 genome wide association studies and 30 association studies were included. 27 studies focused on the Val66Met polymorphism (rs6265), the Met allele being associated with a higher antidepressant efficacy only in Asian patients. Other *BDNF/TRKB/P75NTR* polymorphisms (*BDNF*: rs7103411, rs7124442, rs908867, rs2049046, rs61888800, rs10501087, rs1491850; *TRKB*: rs10868223, rs11140778, rs1565445, rs1659412; *P75NTR*: rs2072446) were reported to be associated with antidepressant efficacy but these results were not replicated. Finally, there are 15 positive studies among 30 studies regarding BDNF/TRKB/P75NTR polymorphisms. The only SNP which benefits of at least 3 positive studies is the BDNF Val66Met polymorphism (rs6265). Consequently, with a lack of good and consistent studies, the clinical utility of BDNF in treatment selection is far from clear.

We propose several recommendations for further studies.

Keywords: BDNF; TRKB; PNTR75; single nucleotide polymorphism; antidepressant response; antidepressant remission; Major Depressive Disorder; Major Depressive Episode

3.3.3 Introduction

Only a third of patients with Major Depressive Episodes (MDE) achieve remission after 3 months of antidepressant treatment [96]. To reduce risks, suffering and minimize costs associated with Major Depressive Disorder (MDD), it is useful to determine criteria that may predict antidepressant efficacy. To the best of our knowledge, these criteria are scarce [97]. Thus, the prediction of response and remission in depressed patients treated with antidepressant drugs remains a challenge for clinicians.

Growing evidence suggests the implication of adult brain plasticity, especially adult hippocampal neurogenesis in antidepressant efficacy [24,27,98,99], especially pharmacogenetic studies focusing on the Brain Derived Neurotrophic Factor (BDNF) and its receptors tyrosine kinase receptor B (TRKB) and p75 neurotrophin receptor (P75NTR) (alternatively named as Nerve Growth Factor Receptor, NGFR or tumor necrosis factor superfamily member 16, TNFRSF16).

The BDNF is a member of the neurotrophin family [100]. The BDNF gene comprises 11 exons that span about 70 kb of chromosome 11 [101]. BDNF, initially synthesized as 32 kD precursor protein called pro-BDNF, is intra- and extra-cellularly cleaved to produce the mature BDNF form [102,103]. Mature BDNF binds to TRKB receptors with high affinity [26,104]. The BDNF/TRKB couple increases neuronal plasticity, such as neurogenesis, neurite arborization, and synaptogenesis. ProBDNF/P75NTR couple lead to programmed neuronal death, neurite retraction, and synaptic pruning [26].

TRKB is mainly present in the central and peripheral nervous system [105,106]. This receptor is located on the cellular membrane and mediates the effects of BDNF through its extra- and intra-cellular domains. It is coded by a 24-exon gene that spans about 24 kb located on chromosome 9 (q22.1) [40,107]. The binding of the BDNF dimer to TRKB induces dimerization and autophosphorylation of TRKB, resulting in sequential phosphorylation in intracellular signaling pathways. The BDNF-activated TRKB signaling pathway increases neuronal plasticity, such as neurogenesis, neurite arborization, and synaptogenesis.

The P75NTR gene comprises 6 exons that span about 23 kb of chromosome 17q21–q22. P75NTR preferentially binds mature pro-BDNF. Pro-BDNF-P75NTR pathway may promote cell death in rodent neurons, oligodendrocytes and Schwann cells [108]. If co-expressed, TrkB and P75NTR work together as a receptor complex for mature BDNF. In this heterodimer, the mature BDNF seems to interact solely with the TRKB component, p75NTR acting indirectly to increase the number of high affinity binding sites for TRKB [109].

Preclinical evidence suggests that the BDNF/TRKB pathway is involved in the pathophysiology of mood disorders and that BDNF-promoted neuronal plasticity underlies the effect of antidepressants. Indeed, in rats, stress induced decrease in BDNF mRNA expression in the hippocampus [33]. And BDNF injections in the dentate gyrus of the hippocampus lead to improvement in depressive behaviors [110]. Similarly, a chronic treatment with antidepressant restores stress-induced changes in BDNF mRNA levels in experimental animals [33,111]. Some preclinical studies also argue for a different impact of BDNF on antidepressant efficacy depending on antidepressant drugs [112-114]. In rodents, TRKB agonists reverse antidepressant like behaviors [115], TRKB is activated by antidepressants [37] and the absence of this receptor in hippocampus cells decrease antidepressant efficacy [38,39].

Clinical studies also point out that BDNF and TRKB receptor density in the brain and BDNF concentrations are decreased in the plasma of suicidal subjects [116,117]. Furthermore, antidepressant treatment increases BDNF levels in the hippocampus of postmortem human brains [118]. In a more recent study, in MDD patients, serum BDNF was decreased during MDE and some data suggests that antidepressants may act by normalizing the levels of serum BDNF [119,120].

Taking into account the growing evidence for BDNF/TRKB/P75NTR involvement in antidepressant efficacy and the need for biomarkers to guide clinical prescription of antidepressant drugs, we propose an extensive review of the literature about the effects of polymorphisms of the BDNF/TRKB/P75NTR signaling pathway on antidepressants efficacy in depressed patients.

3.3.4 Methods

We reviewed the literature by an extensive PUBMED search of studies published until December 2014. Firstly, we used PUBMED SNP to identify published single-nucleotide polymorphisms (SNPs) for the BDNF, TRKB and PNTR75 genes. Only SNP studies involving antidepressant drugs were selected for this review. Secondly, we checked the references of all included studies to identify supplementary data. Thirdly, we screened each SNP as keyword "rs..." in PUBMED to identify further studies. Finally, to be included in this review, studies had to be 1) clinical prospective studies, 2) with clinical assessment at baseline and at the end of the follow-up period and 3) of patients with a diagnosis of MDE (DSM criteria) either MDD or Bipolar and treated with antidepressant drugs (all marketed antidepressant drugs could be included).

The screening of studies was performed independently by two investigators (RC and SM for BDNF/P75NTR and ED and SM for TRKB). In case of disagreement, the relevance of the study was assessed consensually by both investigators. Thus, 37 studies were initially selected and four studies were excluded, two because of the absence of pharmacological treatment, another because it did not focus on antidepressant efficacy and the last one for statistical methodological limitations.

Overall, 5 genome wide association studies (GWAS) (including one meta-analysis) and 30 pharmacogenetic association studies (methodology in **table 3**) were included in this review.

Levels of evidence for each SNP were estimated individually based on the “clinical annotation level of evidence” of PharmGKB

(<https://www.pharmgkb.org/page/clinAnnLevels>) described in **Supplemental table S6**.

Extrapolations of this assessment scale were also propose to estimate the level of evidence for haplotype associations.

*

Study	n (included)	Ethnicity	Diagnosis	Bipolar	Cohorte Name	Follow up (w)	AD	Dose (mg/d)	Design	Scale	Outcome	ref
Tsai et al., 2003	152	Asian	MDE-MDD	not applicable		4	F	20-60	prospective open	HAMD	response/remission	[121]
Choi et al., 2006	128	Asian	MDE-MDD	not applicable		8	C	10-60	prospective open	HAMD	response	[122]
Wilkie et al., 2007	166	Caucasian	MDE-MDD	excluded		6-12	P/C//L/Ph		prospective open	HAMD	response/remission	[123]
Gratacos et al., 2008	374	Caucasian	MDE	40 %		6	F/P/S/C/V	20-40/20-40/100-200/20-40/150-300	prospective open	HAMD	remission	[124]
Lin et al., 2008	72	Asian	MDE-MDD	not applicable		4	V	75-150	prospective open	HAMD	response	[125]
Yoshida et al., 2008	134	Asian	MDE-MDD	not applicable		6	Fv/MI	50-200/50-100	prospective open	MADRS	score/response	[126]
Gau et al., 2008	228	Asian	MDE-MDD	excluded		8	F	20-40	prospective open	HAMD	score/response	[127]
Dong et al., 2009	272	Mexican American	MDE-MDD	excluded	UCLA PPRG	8	F/D	10-40/50-200	randomized double blind	HAMD	score/remission	[40]
Licinio et al., 2009	272	Mexican American	MDE-MDD	excluded	UCLA PPRG	8	F/D	10-40/50-200	randomized double blind	HAMD	score/remission	[128]
Alexopoulos et al., 2010	34	Caucasian	geriatric MDE-MDD	excluded		12	E	10	prospective open	HAMD	remission	[129]
Bukh et al., 2010	290	Caucasian	MDE-MDD	excluded		52	all marketed AD		prospective open	HAMD	score	[130]
Domschke et al., 2010	268	Caucasian	MDE-MDD	excluded	Muenster	6	all marketed AD		prospective open	HAMD	score	[131]
Kang et al., 2010	243	Asian	MDE-MDD	not applicable		8	M	15-60	prospective open	HAMD	score/response	[132]
Lancot et al., 2010	90	Caucasian	MDE-MDD	excluded		6	C	20	prospective open	HAMD	score/response/remission	[133]
Pae et al., 2010	141	Asian	MDE-MDD	not applicable		5	all marketed AD		prospective open	MADRS	remission	[134]
Zou et al., 2010	305	Asian	MDE-MDD	not applicable		6	F	20	prospective open	HAMD	score/response/remission	[135]
Kocabas et al., 2011	206	Caucasian	MDE-MDD	excluded	PTRSSUAD	4	all marketed AD		prospective open	HAMD	response/remission/resistance	[136]
Su et al., 2011	166	Asian	Alcohol + MDE-MDD	excluded		8	S	150	prospective open	HAMD	response	[137]
Taylor et al., 2011	229	Caucasian	geriatric MDE-MDD	not applicable		26	all AD		prospective open	MADRS	score/remission	[138]
Yoshimura et al., 2011	132	Asian	MDE-MDD	not applicable		8	P/S	20-40/25-100	prospective open	HAMD	response	[139]
Katsuki et al., 2012	84	Asian	MDE-MDD	not applicable		4	M	na	prospective open	na	na	[140]
Musil et al., 2012	324	Caucasian	MDE	Frequency not specified		6	all marketed AD		prospective open	HAMD	score/response	[141]
Xu et al., 2012	159	Asian	MDE-MDD	not applicable		4	SSRI/V	na	prospective open	HAMD	score/response	[142]
Hennings et al., 2013	894	Caucasian	MDE	11%	MARS/Muenster	5	all marketed AD		prospective open	HAMD	score/response/remission	[41]
Illi et al., 2013	106	Caucasian	MDE-MDD	excluded		6	C/F/P	na	prospective open	MADRS	response/remission	[143]
Li et al., 2013	948	Asian	MDE-MDD	excluded		12	all marketed AD		prospective open	HAMD	resistance	[42]
El Hage et al., 2014	187	Caucasian	MDE	15%		3-6	E	10-30	prospective open	MADRS	score/response/remission	[144]
Liu et al., 2014	155	Asian	MDE with CD	na		8	S	na	prospective open	na	na	[145]
Matsumoto et al., 2014	97	Caucasian	MDE-MDD	excluded		8	all marketed AD	na	prospective open	na	na	[146]
Colle et al., 2015	345	Caucasian	MDE-MDD	excluded		26	SSRI/SNRI/TCA	na	prospective open	HAMD	response/remission	[147]

Table 3 : Characteristics of included studies.

AD: Antidepressant; C: Citalopram; CD: Coronary disease; D: Desipramine; E: Escitalopram; F: Fluoxetine; Fv: Fluvoxamine; I: Imipramine; L: Lofepamine; M: Mirtazapine; MDD: Major depressive disorder; MDE: Major depressive episode; MI: Minalcipran; NA: Not available; P: Paroxetine; Ph: Phenelezine; S: Sertraline; SNRI: Serotonin and norepinephrine reuptake inhibitor; SSRI: Serotonin selective reuptake inhibitor; TCA: Tricyclic antidepressant; V: Venlafaxine; w: Weeks.

3.3.5 Results

GWAS

We identified four GWAS studies: Uher et al., 2010 [148] (GENDEP, n =706), Ising et al., 2009 [149] (MARS, n=339 + German replication sample, n=361), Garriock et al., 2010 [150] (STAR*D, n= 1948), Ji et al., 2013 [151] (PGRN-AMPS, n= 529). None of these studies reported SNP of BDNF/TRKB/P75NTR associated with antidepressant efficacy. Accordingly, a meta-analysis of 3 GWAS (STAR*D, GENDEP and MARS) [152] including 1.2 million of SNP in 2,256 individuals of Northern European descent with MDD, receiving antidepressant treatment for at least 12 weeks, failed to identify SNP of BDNF/TRKB/P75NTR associated with antidepressant efficacy.

BDNF POLYMORPHISMS

84 SNPs are reported in the literature, of which 37 were never explored for antidepressant efficacy. The 47 others were explored: a significant association was shown for eight of them whereas there is no reported association for the 39 others. Among the 37 which were never explored for antidepressant efficacy, three were located in an exonic region and concern missense mutations (rs1048218, rs1048220 and rs1048221), fifteen were localized in intronic regions (rs11030107, rs11030108, rs11030118, rs11030119, rs12291063, rs12291186, rs16917234, rs1967554, rs2030323, rs2049045, rs2049046, rs56164415, rs6484320, rs7127507, rs7934165), one was in 5'UTR (rs28383487) region, one in 3'UTR (rs11030100) and, for seventeen SNPs, the locations were unknown (rs10835187, rs11030064, rs1157659, rs1387145, rs1519480, rs2203877, rs2352802, rs2883187, rs3750934, rs3763965, rs4074134, rs4923461, rs4923463, rs7481311, rs8192466, rs972096, rs988712). These 47 SNPs were extracted from 28 association studies, were assessed for their association with antidepressant efficacy in MDD (**Table 4**)

Study	SNP	Location	Biological Effect	Minor Allele	MAF	n	Ethnicity	Diagnosis	AD	Genotype with higher efficacy	Significant Outcome	L.E.	Ref			
Gratacos et al., 2008	rs10501087	3' UTR	Unknown	C	0.26	374	Caucasian	MDE	F/P/S/C/V	no	no	3	[124]			
Kocabas et al., 2011				na	na	206	Caucasian	MDE-MDD	all marketed AD	C	Response : OR=2.06 95%CI (1.23–3.45), p=0.009	3	[136]			
Gratacos et al., 2008	rs1491850	5'UTR	Unknown	C	0.43	374	Caucasian	MDE	F/P/S/C/V	no	no	3	[124]			
Kocabas et al., 2011				na	na	206	Caucasian	MDE-MDD	all marketed AD	C	Response : OR=1.88 95%CI (1.23–2.88), p=0.007	3	[136]			
Hennings et al., 2013	rs2049046	intron	Unknown	C	na	894	Caucasian	MDE	all marketed AD	no	no	3	[41]			
Hennings et al., 2013				A	na	894	Caucasian	MDE	all marketed AD	T	Response : p=0.02	3	[41]			
Licinio et al., 2009	rs61888800	intron	Unknown	na	na	272	Mexican American	MDE-MDD	F/D	GG	Response : p=0.02	3	[128]			
Illi et al., 2013				T	0.25	106	Caucasian	MDE-MDD	C/F/P	no	no	3	[143]			
Tsai et al., 2003	rs6265	exon missense	Met= Decrease dendritic trafficking	Met	0.54	152	Asian	MDE-MDD	F	no	no	3	[121]			
Choi et al., 2006				Met	0.54	128	Asian	MDE-MDD	C	Met	Score : p=0.03 Response : OR=4.375, 95%CI (1.61–11.9), p=0.003	3	[122]			
Wilkie et al., 2007				Met	0.16	166	Caucasian	MDE-MDD	P/C/IL/Ph	no	no	3	[123]			
Gratacos et al., 2008				Met	0.23	374	Caucasian	MDE	F/P/S/C/V	no	no	3	[124]			
Lin et al., 2008				Met	0.51	72	Asian	MDE-MDD	V	no	no	3	[125]			
Yoshida et al., 2008				Met	0.41	134	Asian	MDE-MDD	Fv/MI	Met	Score : p=0.0004	3	[126]			
Licinio et al., 2009				Met	0.10	272	Mexican American	MDE-MDD	F/D	no	no	3	[128]			
Alexopoulos et al., 2010				Met	0.28	34	Caucasian	geriatric MDE-MDD	E	Met	Remission : p=0.04	3	[129]			
Bukh et al., 2010				Met	na	290	Caucasian	MDE-MDD	all marketed AD	no	no	3	[130]			
Domschke et al., 2010				Met	0.20	268	Caucasian	MDE-MDD	all marketed AD	no	no	3	[131]			
Kang et al., 2010				Met	0.52	243	Asian	MDE-MDD	M	no	no	3	[132]			
Lanctot et al., 2010				Met	0.19	90	Caucasian	MDE-MDD	C	Val/Val	Score : 0.02	3	[133]			
Pae et al., 2010				Met	0.48	141	Asian	MDE-MDD	all marketed AD	no	no	3	[134]			
Taylor et al., 2011				Met	na	229	Caucasian	geriatric MDE-MDD	all marketed AD	Met	Remission : p=0.049	3	[138]			
Zou et al., 2010				Met	0.48	305	Asian	MDE-MDD	F	no	no	3	[135]			
Kocabas et al., 2011				na	na	206	Caucasian	MDE-MDD	all marketed AD	Met	Response : OR=2.07, 95%CI (1.22–3.51), p=0.01	3	[136]			
Su et al., 2011				Met	0.53	166	Asian	Alcohol+MDE-MDD	S	Met	Response : OR=2.17, 95%CI (1.39-3.42), p=0.001	3	[137]			
Yoshimura et al., 2011				Met	0.35	132	Asian	MDE-MDD	P/S	no	no	3	[139]			
Katsuki et al., 2012				na	na	84	Asian	MDE-MDD	M	no	no	3	[140]			
Musil et al., 2012				Met	0.19	324	Caucasian	MDE	all marketed AD	no	no	3	[141]			
Xu et al., 2012				Met	na	159	Asian	MDE-MDD	SSRI 104/V 55	Met	SSRI: Score: p=0.02 SSRI: Response: OR=4.85, 95%CI (1.04-22.58), p=0.04	3	[142]			
Hennings et al., 2013				Met	na	894	Caucasian	MDE	all marketed AD	no	no	3	[41]			
Li et al., 2013				Met	0.48	948	Asian	MDE-MDD	all marketed AD	no	no	3	[42]			
El Hage et al., 2014				Met	0.25	187	Caucasian	MDE	E	Met	Response : p=0.02	3	[144]			
Liu et al., 2014				na	na	155	Asian	MDE with CD	S	Met	Response : OR=2.14, 95%CI (1.29-3.53), p=0.003	3	[145]			
Matsumoto et al., 2014				Met	0.24	97	Caucasian	MDE	all marketed AD	no	no	3	[146]			
Colle et al., 2015				Met	0.19	345	Caucasian	MDE-MDD	SSRI/SNRI/TCA	Met Val/Val	SSRI: Response: OR: 3.04, 95%CI (1.05-9.37), p=0.04 SNRI/TCA: Remission: OR=0.27, 95%CI (0.09; 0.76), p=0.02	3	[147]			
Domschke et al., 2010				rs7103411	intron	Unknown	C	0.22	268	Caucasian	MDE-MDD	all marketed AD	C	Score: Male: p=.009, Anxious: p=0.005 Melancolic: p=0.003	3	[131]
Musil et al., 2012							C	0.22	324	Caucasian	MDE-MDD	all marketed AD	no	no	3	[141]
Licinio et al., 2009				rs7124442	exon	Unknown	C	0.23	272	Mexican American	MDE-MDD	F/D	no	no	3	[128]
Domschke et al., 2010							C	0.31	268	Caucasian	MDE-MDD	all marketed AD	CC	Score : p=0.01	3	[131]
Musil et al., 2012				rs908867	5' UTR	Unknown	C	0.28	324	Caucasian	MDE	all marketed AD	no	no	3	[141]
Gratacos et al., 2008	A	0.07	374				Caucasian	MDE	F/P/S/C/V	A	Remission : OR=3.57, 95%CI (1.51–8.16), p=0.003	3	[124]			
Kocabas et al., 2011	rs908867	5' UTR	Unknown	na	na	206	Caucasian	MDD-MDD	all marketed AD	no	no	3	[136]			
Licinio et al., 2009				A	0.04	272	Mexican American	MDE-MDD	F/D	no	no	3	[128]			

Table 4 : BDNF SNPs associated with antidepressant efficacy

AD: Antidepressant; C: Citalopram; CD: Coronary disease; D: Desipramine; E: Escitalopram; F: Fluoxetine; Fv: Fluvoxamine; I: Imipramine; L: Lofepamine; L.E.: Level of evidence; M: Mirtazapine; MAF: Minor allele frequency; MDD: Major depressive disorder; MDE: Major depressive episode; MI: Minalcipran; NA: Not available; OR: Odds ratio; P: Paroxetine; Ph: Phenezepine; S: Sertraline; SNRI: Serotonin and norepinephrine reuptake inhibitor; SSRI: Serotonin selective reuptake inhibitor; TCA: Tricyclic antidepressant; V: Venlafaxine; w: Weeks.

Historically, the first studies assessed the functional Val66Met polymorphism. Other ones investigated other gene locations with a systematic approach. For the first time Licinio et al. [128] investigated together exonic, intronic, 3'UTR and 5'UTR region with a complete sequencing approach. Kocabas et al. [136] focused on 3'UTR and 5'UTR regions.

Only the study of Licinio et al. [128] was a randomized double-blind controlled trial. Since MDE occur mainly in MDD but also in Bipolar disorders, and because response to antidepressants may differ between MDD and Bipolar disorder, this point was examined carefully: 12 studies had explicit exclusion criteria for Bipolar disorders. 9 studies focused on MDD but did not exclude explicitly bipolar disorders. Bipolar disorders were included in 4 studies (frequency: 11- 40%). Ethnicity was also heterogeneous: 13 studies focused on Asian patients and 14 on Caucasians patients. 8 studies focused on selective serotonin reuptake inhibitor (SSRI), one on venlafaxine (SNRI) and two on mirtazapine. In the others, several classes of antidepressant drugs were assessed. Except six studies with a duration longer than 12 weeks, most studies were short term ones (4 to 8 weeks).

Polymorphisms with no reported association

We show the 39 SNPs with no association with antidepressant efficacy in **Supplemental table S7**.

Polymorphisms with a reported positive association

Table 4 shows the 8 SNPs with a reported association with antidepressant efficacy (level of evidence of 3).

rs6265

The most studied *BDNF* polymorphism is the Val66Met (rs6265) (Valine is changed by Methionine in the 66 position of BDNF protein). To the best of our knowledge, this is the only SNP with a reasonably known functional biological effect, the Met allele being associated with a decreased dendritic trafficking [153]. This functional polymorphism is assessed in 26 MDE samples. Some studies suggest an association between the Val66Met polymorphism and response or remission with antidepressant drugs, either in Asian [122,135,142] or in Caucasian patients [129,133,138,144]. However, several studies failed to replicate this association, both in Asian [42,121,125,126,132,134,140,145] and in Caucasian [41,124,128,130,131,136,138,141,146] patients, including the powerful study

comprising the STAR-D results [131]. Meta-analyses [154-156] pointed out either a higher response rate in Met patients that may be specific to Asian patients, or no difference in response and remission rates between Met and Val/Val Caucasian patients. The meta-analysis of Niitsu et al. [157] including 10 studies (8 of Asian patients [121,122,126,132,135,137,139,158], one study of Caucasian patients [123] and data from STAR-D) showed that in Asian patients, the Met allele is associated with a higher antidepressant efficacy (level 2B). In Caucasian patients however, the Val66Met effect remains unclear. As the frequency of the Met66 allele is different between Caucasian (16-28%) and Asian (35-54%) populations, the functionality could be different in these populations. Moreover, some differences may exist between antidepressants. Licinio et al. [128] found no different effect between fluoxetine (n=97) and desipramine (n=103). However, Xu et al. [142] found a higher 4-week antidepressant efficacy in Met carriers treated with SSRI (n=104) but not with venlafaxine (n=55). In a recent study we reported [147] interactions between the Val66Met polymorphism and antidepressant drug classes: With SSRI, Val/Val patients had a higher response rate than Met patients. With SNRI/TCA, Val/Val patients had a lower remission rate than Met patients.

Other BDNF genetic polymorphisms

For the other *BDNF* SNPs associated with antidepressant efficacy, to the best of our knowledge, there is no biological effect documented and none of these associations were replicated (level 3). For example, the rs2049046 polymorphism was assessed in one study and was associated with antidepressant efficacy (level 3) [41], however, the promising effect of this polymorphism needs to be replicated in further studies.

6 SNPs are associated with antidepressant efficacy, but they were not replicated in other studies (level 3). Indeed, for rs61888800 (intronic polymorphism), Licinio et al. [128] showed that the GG genotype was associated with a higher efficacy but this was not replicated by Illi et al. [143] (level 3). For rs7103411, the TT genotype was associated with a lower antidepressant efficacy [131], but this result was not replicated in a second study [141]. For rs7124442 (a missense exonic mutation), the TT genotype was associated with a higher antidepressant efficacy [131], but this result was not replicated in two other papers [128,141] (level 3). For rs1491850 (5'UTR), the C allele was associated with a higher antidepressant efficacy [136], but this result was not replicated in a second study [41] (level 3). For rs908867 (5'UTR), the A allele was associated with a higher antidepressant efficacy [124], but this result was not replicated in two other studies [128,136]. Finally the C allele of

rs10501087 (3'UTR) was associated with a higher antidepressant efficacy [136] but was also not replicated in a second study [124] (level 3).

BDNF haplotype analyses

Table 5 shows results about BDNF haplotype* analyses. Five haplotypes were associated with antidepressant efficacy.

Study	Haplotype	n	Ethnicity	Diagnosis	AD	Results	L.E.	Ref.
Domschke et al., 2010	rs7103411-rs6265-rs7124442	268	Caucasian	MDE-MDD	all marketed AD	T-Val-T: lower efficacy : p=0.005	3	[131]
Kocabas et al., 2011	rs10501087-rs6265-rs1491850	206	Caucasian	MDE-MDD	all marketed AD	T-Val-T : response/ resistance	3	[136]
Hennings et al., 2013	rs1030094-rs11602246	894	Caucasian	MDE	all marketed AD	G-C : higher efficacy : p=0.007	3	[41]
Hennings et al., 2013	r6265-rs11030109-rs10835211-rs2049046-rs4923468-rs12273363	894	Caucasian	MDE	all marketed AD	G-G-G-A-C-T : lower efficacy : p=0.007	3	[41]
Gratacos et al., 2008	rs12273363-rs908867-rs1491850	374	Caucasian	MDE	F/P/S/C/V	T-A-T : higher remission rates: OR=2.71; 95%CI (1.305.63), p=0.008	3	[124]

Table 5 : BDNF haplotypes associated with antidepressant efficacy.

AD: Antidepressant; C: Citalopram; F: Fluoxetine; L.E.: Level of evidence; MDD: Major depressive disorder; MDE: Major depressive episode; OR: Odds ratio; P: Paroxetine; S: Sertraline; V: Venlafaxine.

Haplotype* : groupe d'allèles de différents loci situés sur un même chromosome et habituellement transmis ensemble.

TRKB POLYMORPHISMS

There were only three studies focusing on 153 TRKB SNPs (**Table 6**). Only one study was a randomized double-blind controlled one [40]. In the two other studies, antidepressants were prescribed in open naturalist designs [41,42]. They were short term (with a maximum of 12-week duration). The samples were heterogeneous regarding ethnicity (Mexican Americans [40], Caucasians [41], and Asian [42]). Hennings et al., 2013 [60] chose SNPs on the minor allelic frequency (MAF>0.1) in the Munich Antidepressant Response signature (MARS) project and two replication samples from MARS sample and the Muenster cohort. Dong et al. [40] selected 89 SNPs in the Vega database, whereas Li et al. [42] selected 3 SNPs from the literature.

Study	SNP	Location	Minor allele	MAF	n	Ethnicity	Diagnosis	AD	Genotype with higher efficacy	Outcome	L. E.	Ref.
Hennings et al., 2013	rs1659412	5' UTR	C	0.10	894	Caucasian	MDE – MDD or bipolar disorder	all marketed AD	C	Response: OR=na, p=0.02	3	[41]
Hennings et al., 2013	rs10868223	intron	T	0.12	894	Caucasian	MDE – MDD or bipolar disorder	all marketed AD	C	Response: OR=na, p=0.02	3	[41]
Hennings et al., 2013	rs11140778	intron	T	0.21	894	Caucasian	MDE – MDD or bipolar disorder	all marketed AD	A	Response: OR=na p=0.004	3	[41]
li et al., 2013	rs1565445	intron	C	0.32	948	Han Chinese	MDE-MDD	all marketed AD	C	Resistance: OR=1.43, 95%IC(1.16–1.76), p=0.0008	3	[42]

Table 6 : TRKB SNPs associated with antidepressant efficacy

AD: Antidepressant; L.E.: Level of evidence; MAF: Minor allele frequency; MDD: Major depressive disorder; MDE: Major depressive episode; NA: Not available; OR: Odds ratio

Polymorphisms with no reported association with antidepressant efficacy

They are presented in **Supplemental table S8**.

Polymorphisms with a reported association with antidepressant efficacy

Table 6 shows the TRKB SNPs associated with antidepressant efficacy in at least one study, corresponding to a level of evidence of 3. None of these positive associations were replicated.

TRKB Haplotype analysis

None of them reported TRKB haplotypes with a significant association (after correction for multiple tests) with antidepressant efficacy [40,41].

P75NTR POLYMORPHISMS

Despite pre-clinical evidence of the relevance of P75NTR in the BDNF/TRKB/P75NTR pathway, we found only one pharmacogenetic study assessing P75NTR impact on antidepressant efficacy in depressed patients [127]. In this study, 5 SNP (rs575791, rs2537706, rs2072446, rs11466155 and rs734194) were assessed in 228 Chinese MDD patients treated in open design with citalopram or fluoxetine for 8 weeks.

And the rs2072446 was associated with a higher response in CC patients ($p=0.04$). The constructed haplotype (rs2072446-rs11466155-rs734194) was associated with response, the TCT patients having a lower response to SSRI ($p=0.01$). The non-synonymous polymorphism may thus contribute to the functional alteration of p75NTR (T carriers). Moreover, other SNPs were described in the literature to have an impact on several conditions like asthma, migraine, Alzheimer disease (rs9908234, rs3785931, rs2072445, rs2072446, rs734194, rs741072, rs10491195) and could be assessed regarding antidepressant efficacy.

BDNF*TRKB POLYMORPHISMS INTERACTIONS

Only two studies investigated possible interactions between BDNF and TRKB on antidepressant efficacy. Hennings et al. [41] showed an interaction between the BDNF SNP rs4923468 and the NTRK2 SNP rs1387926. Li et al. [42] used an original method to explore interactions between three TRKB SNP (rs1387923-rs1565445-rs2769605) and one BDNF SNP (rs6265) and evidenced a 57.4% accuracy for the four-SNP model.

3.3.6 Discussion

Globally, there are 15 positive studies among 30 studies regarding BDNF/TRKB/P75NTR polymorphisms and their association with antidepressant efficacy in depressed patients. For BDNF polymorphisms, 8 out of 47 (17%) polymorphisms studied seem to be significantly associated with antidepressant efficacy, of which 3 are intronic. The only, SNP which benefits of at least 3 positive studies is the BDNF Val66Met polymorphism (rs6265). The results show that the Met allele is associated with a higher antidepressant efficacy in Asian MDD patients (Level of Evidence 2B). 7 other polymorphisms may be also associated with antidepressant efficacy: rs1491850, rs10501087, rs61888800, rs7124442, rs7103411, rs908867 and rs2049046 but were not replicated. In positive studies, the effect sizes were small to moderate (OR comprised between: 1.88 and 4.85).

Some evidence argues for a different impact of BDNF polymorphisms depending on antidepressant drugs. These data are in line with some preclinical ones. Met carrier mice responded to desipramine, a tricyclic antidepressant, but not to an SSRI [114]. However, clarifications about the influence of genetic variant BDNF on monoaminergic transporters would be useful. Indeed, the impact of the Met allele on 5-HTT expression or on the density of serotonergic neurons [159] was not replicated recently [160]. Furthermore, an increased BDNF protein expression in the frontal cortex was observed with SNRIs but not with SSRIs [112,113]. Moreover, a chronic treatment with a SNRI, but not a SSRI, can reduce mature BDNF in the cytosol and increase its level in the crude synaptosomal fraction, suggesting that SNRIs, but not SSRIs, not only produce a marked upregulation of BDNF mRNA and protein, but may also affect the subcellular redistribution of the BDNF [112].

Even if some studies in this field are negative [41,139,140] further studies assessing serum BDNF as a possible proxy of central BDNF concentration and antidepressant efficacy may improve the understanding of the biological effect of these genetic polymorphisms.

For the TRKB 4 SNPS, rs11140778, rs10868223, rs1659412 and rs1565445, of which 3 are intronic were associated with a higher antidepressant efficacy, but none of these associations were replicated.

For the p75NTR gene, only one positive study is available (rs2072446).

In the absence of replication, the clinical and biological significance of these data is doubtful. However, these polymorphisms could be in linkage disequilibrium with others which could have relevant biological effects. Only one of them (BDNF rs2049046) was found to be in linkage disequilibrium with rs6265. So, it is probably not its effect but the effect of Val66Met which is observed here. For other intronic polymorphisms, different possible biological mechanisms to

explain their association with antidepressant efficacy could be suggested, such as alternative splicing, transcription regulation, translation regulation or epigenetic changes.

Limitations

Some limitations exist in the field of genetic approaches. In GWAS, the high number of SNPs studied leads to increased significance level and decreased power. Indeed, these studies are designed to detect the effects of frequent SNPs. In the meta-analysis [152], a satisfying power exists only for SNPs with allelic frequency upper 0.25. However, the TRKB/BDNF/p75NTR SNPs associated with antidepressant efficacy have frequently lower minor allelic frequency. Some authors suggest that future GWAS should need samples of tens thousands patients rather than the thousands usually studied [89]. Additionally, the available genotyping platforms are able to provide only a relatively narrow genomic coverage (for example, less than 50% in the STAR*D) [161].

Some limitations exist in the field of methodology of clinical studies as well. The majority of studies are based on small and heterogeneous samples of patients. In terms of diagnoses, because MDD and Bipolar disorder could be different in terms of antidepressant response, this heterogeneity in the samples studied could impact the results. Efficacy of antidepressant drugs may also differ between bipolar and unipolar patients. Moreover, there is a possible different impact of genetic polymorphisms with different types of antidepressant drugs. This point could be a confounding factor. Ethnicity or treatment duration should also be taken into account.

Another limitation is that the biological consequences of the SNPs are not well known in humans.

Last, but not least, publication biases are a major limitation of this review. Publication biases are frequent in the medical literature, positive studies being as much as 3 times more likely to be published than negative studies [162]. This is a limitation of this review, in which the positive results could be overestimated as compared to the whole data obtained in this field [162].

Future Perspectives

In terms of clinical perspectives, we recommend well characterized and homogenous phenotypes: either MDD or Bipolar disorders, or both MDD and Bipolar disorders with separate analyses. Accordingly, ethnicity should be precisely described, and if mixed ethnicity populations are included, they should be analyzed separately. We also recommend that further studies have longer than 3 months duration. The more frequently used designs are prospective

naturalistic cohorts with blind genotype assessment. Actually, a placebo-controlled RCT to assess polymorphism effects on antidepressant efficacy is usually not performed for ethical reasons. Moreover, patients in RCT are quite selected and non-representative of real life patients. And, if positive results could be found in a RCT, these results would have to be confirmed in naturalistic designs to assess their clinical relevance in daily clinical practice. In this context, adding a randomization to a longitudinal open cohort, as did Licinio et al. [128] and Dong et al. [40] appears to be a good compromise.

In terms of genetic and biological perspectives, even if the expected effect size could be rather small, 37 BDNF SNPs described in the literature, not yet studied for antidepressant efficacy, should be studied, especially the 3 exonic missense SNPs, and the TRKB and p75NTR genes. Moreover, although BDNF/TRKB/PNTR75 interacts with the monoamine system which may affect the clinical response to antidepressants, the interaction between the BDNF/TRKB/PNTR75 gene and genes related to the monoamine or glutamatergic systems on antidepressant efficacy should be studied.

Biological indices such as BDNF serum, LCR BDNF or brain imaging markers could also be helpful to better understand the role of SNPs on antidepressant efficacy. BDNF expression which is also regulated by epigenetic chromatin remodeling, including DNA methylation, histone acetylation, and other chemical alterations in gene promoter regions should also be studied, since an increase in CpG methylation at promoter regions on the BDNF gene was correlated with decreased synthesis of BDNF in neurons [163].

Moreover, the involvement of common functional variants in antidepressants drug response, specifically of brain methylations sites, was described recently by Wong et al. [164]. Interestingly, those results support some previous works on the influence of variation in DNA methylation. Indeed, in the central nervous system, DNA methylation of cytosines in cytosine–guanine (CpG) dinucleotides is regarded as the representative component of broader epigenetic modification at a given locus [165], and suggesting that the consequence of those epigenetic markers could be more investigated, particularly during pregnancy [166], and human studies developmentally sensitive to the quality of the environment [167,168].

However, as with other psychiatric disorders, the genetics of MDD and antidepressant efficacy is complex. Genetic risk factors with individually large effects are likely to be rare. Association based methods to identify common genetic risk alleles in MDD presented limited success. Genome Wide Association studies based on common genetic variants have yielded relatively few candidate genes that not confirmed by replication. Alternative approaches that focus on rare genetic variants are needed. One genetic approach that was used effectively to overcome some problems of heterogeneity is the genome wide analysis of copy-number variants (CNVs).

Current genotyping platforms and CNV discovery algorithms enable the genotyping of copy number polymorphisms (CNPs) and the analysis of CNVs. CNVs are submicroscopic deletions and duplications in genomic DNA that were implicated in variety of different psychiatric disorders. Interestingly, studies from multiple groups have now firmly established that rare CNVs contribute to genetic risk for schizophrenia, autism spectrum disorder, MDD and, in particular, that spontaneous CNVs are important risk factors in the sporadic form of the disorders [169-172]. Moreover, recently, Tansey et al. [173] found that specific CNVs were nominally associated with poor response to antidepressants in MDD patients.

One of the most interesting as well as challenging observations has been the degree of phenotypic variability associated with individual CNVs, i.e, the “expressivity” of the genotype. Undoubtedly, the phenotypic expression of rare high penetrance alleles is modulated by other genetic factors, including rare variants, as well as common (polygenic) variation [174] or epigenetic regulation [164,175].

Since the effects of SNPs alone may be rather limited, integration of several biomarkers could be relevant. And composite scores using Gene*Gene interaction or Gene*Biomarker interaction could be useful to predict antidepressant efficacy.

3.3.7 Conclusion

Finally, there are 15 positive studies among 30 studies regarding BDNF/TRKB/P75NTR polymorphisms and their association with antidepressant efficacy in depressed patients. The only, SNP which benefits of at least 3 positive studies is the BDNF Val66Met polymorphism (rs6265). Moreover, studies suffer from methodological limitations. Consequently, with a lack of good and consistent studies, the clinical utility of BDNF in treatment selection is far from clear.

3.3.8 Article 3

Cette partie est l'étude proprement dite dans la cohorte METADAP. Nous avons étudié l'influence de 8 polymorphismes du TRKB sur la réponse thérapeutique après traitement par antidépresseur chez des patients avec un EDC dans le cadre d'un TDU.

Cette recherche a fait l'objet d'un article publié dans Pharmacogenomics, le texte est présenté en anglais tel qu'il est publié.

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Pharmacogenomics



No impact of eight NTRK2 genetic polymorphisms on 6-month antidepressant efficacy in depressed patients

Aim: NTRK2 is the main receptor of the brain derived neurotrophic factor, which is involved in antidepressant efficacy. We assessed the impact of eight NTRK2 SNPs pertaining to response and remission after antidepressant treatment in depressed patients. **Patients & methods:** In a naturalistic study, 569 patients with a major depressive episode requiring a new antidepressant treatment were genotyped for eight NTRK2 SNPs (rs1187352, rs1439050, rs1778933, rs2289656, rs2289657, rs2289658, rs3824519, rs56142442) and prospectively assessed for response and remission after 6 months of treatment. **Results:** No association was shown between the NTRK2 SNPs and response/remission. **Conclusion:** There is no benefit to assess these eight TRKB SNPs to predict response/remission after antidepressant treatment in depressed patients.

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Keywords: antidepressant • genetic polymorphism • major depressive disorder • major depressive episode • NTRK2 • pharmacogenetics • remission • response • TRKB

Half of the patients with major depressive episodes (MDE) in major depressive disorder (MDD) do not respond to antidepressant treatment, while two-thirds do not achieve remission after 3 months [1]. Identifying biomarkers at baseline for future response and remission after administering antidepressant medication, could improve the efficacy of treatment for depressed patients [2]. Among these potential biomarkers, pharmacogenetic biomarkers are particularly interesting in a personalized medicine approach [3].

NTRK2 is the main receptor of BDNF, which is involved in antidepressant efficacy [4,5]. Its activation by BDNF increases neuronal survival, plasticity, neurogenesis and synaptic connectivity [6]. In preclinical studies, NTRK2 is indirectly activated by antidepressants and some NTRK2 agonists have antidepressant effects [4]. Moreover, the lack of this receptor in hippocampal cells decreases antidepressant efficacy [4,7]. In human stud-

ies some NTRK2 genetic polymorphisms are associated with an increased risk of depression [8–10]. And the impact of some NTRK2 SNPs on response or remission, after antidepressant treatment, has been assessed in depressed patients [11–14] (Table 1). In particular, Dong *et al.* [11] showed an association between rs2289656, rs2289657, rs2289658 and rs56142442 and the 8-week response and remission rates after antidepressant treatment in a sample of 272 Mexican–American depressed patients. However, due to the high number of genetic variants assessed in this study and the sample size, these NTRK2 SNPs did not reach statistical significance after correction for multiple tests. Furthermore, in this study, the allelic frequencies of these SNPs differed regarding ethnicity: the minor allelic frequencies of rs2289656, rs2289657 and rs2289658 in Mexican–Americans versus Caucasians were respectively: 9 versus 17%, 10 versus 6% and 15.6 versus 4% [15].



3.3.9 Abstract

Aim: NTRK2 is the main receptor of the brain derived neurotrophic factor, which is involved in antidepressant efficacy. We assessed the impact of eight NTRK2 SNPs pertaining to response and remission after antidepressant treatment in depressed patients.

Patients & methods: In a naturalistic study, 569 patients with a major depressive episode requiring a new antidepressant treatment were genotyped for eight NTRK2 SNPs (rs1187352, rs1439050, rs1778933, rs2289656, rs2289657, rs2289658, rs3824519, rs56142442) and prospectively assessed for response and remission after 6 months of treatment.

Results: No association was shown between the NTRK2 SNPs and response/remission.

Conclusion: There is no benefit to assess these eight TRKB SNPs to predict response/remission after antidepressant treatment in depressed patients.

3.3.10 Introduction

Half of the patients with major depressive episodes (MDE) in major depressive disorder (MDD) do not respond to antidepressant treatment, while two-thirds do not achieve remission after 3 months [96]. Identifying bio-markers at baseline for future response and remission after administering antidepressant medication, could improve the efficacy of treatment for depressed patients [176]. Among these potential bio-markers, pharmacogenetic biomarkers are particularly interesting in a personalized medicine approach [177].

NTRK2 is the main receptor of BDNF, which is involved in antidepressant efficacy [26,39]. Its activation by BDNF increases neuronal survival, plasticity, neurogenesis and synaptic connectivity [95]. In preclinical studies, NTRK2 is indirectly activated by antidepressants and some NTRK2 agonists have antidepressant effects [26]. Moreover, the lack of this receptor in hippocampal cells decreases antidepressant efficacy [38,95]. In human studies some NTRK2 genetic polymorphisms are associated with an increased risk of depression [35,178,179]. And the impact of some NTRK2 SNPs on response or remission, after antidepressant treatment, has been assessed in depressed patients [15-17,20,40-42,95] (**Table 7**). In particular, Dong et al. [40] showed an association between rs2289656, rs2289657, rs2289658 and rs56142442 and the 8-week response and remission rates after antidepressant treatment in a sample of 272 Mexican–American depressed patients. However, due to the high number of genetic variants assessed in this study and the sample size, these NTRK2 SNPs did not reach statistical significance after correction for multiple tests. Furthermore, in this study, the allelic frequencies of these SNPs differed regarding ethnicity: the minor allelic frequencies of rs2289656, rs2289657 and rs2289658 in Mexican–Americans versus Caucasians were respectively: 9 versus 17%, 10 versus 6% and 15.6 versus 4% [180].

Hence, our primary aim was to assess the association of these NTRK2 SNPs with response and remission after antidepressant treatment in a larger population of depressed patients. Our second aim was to assess the same association in the homogeneous ethnic sample of Caucasian patients.

Study (year)	Patients (n)	Ethnicity	Diagnosis	Bipolar patients	Cohort Identification	Follow-up (week)	Antidepressant	Design	Outcomes	SNPs studied (n)	SNPs associated with AD efficacy	Ref.
Dong et al. (2009)	142	Mexican–American	MDE MDD	Excluded	UCLA PPRG	8	Fluoxetine (n = 74) Desipramine (n = 68)	Double-blind randomized controlled	HAMD Improvement Remission	89	rs2289656 rs2289657 rs2289658 rs56142442	[40]
Hennings et al., 2013	894	Caucasian	MDE MDD/BD	11%	MARS/ muenster	5	All marketed AD	Prospective open	HAMD Response	64	rs1659412 rs10868223 rs11140778	[37][41]
Li et al., 2013	948	Asian	MDE MDD	Excluded	OPERATION/ CARE	12	SSRI (n = 603) SNRI (n = 267) Others (n = 78)	Prospective open	HAMD Resistance	3	rs1565445	[42]

Table 7 : Published studies with NTRK2 NPs and outcome after antidepressant treatment in depressed patients

AD: Antidepressant; BD: Bipolar disorder; HAMD: Hamilton Depression Rating Scale; MDD: Major depressive disorder; MDE: Major depressive episode; Remission: Hamilton Depression Rating Scale <8; Resistance: lack of response after two or more trials of antidepressants from different classes with adequate dosages and treatment durations; Response: At least 50% reduction of Hamilton Depression Rating Scale; SNRI: Serotonin and norepinephrine reuptake inhibitor; SSRI: Selective serotonin reuptake inhibitor.

3.3.11 Patients & Methods

Design

In a 6-month prospective, real-world treatment study in psychiatric settings [50], patients with a current MDEs were assessed at the beginning of antidepressant treatment, as well as 1, 3 and 6 months later. Clinical assessments were performed blind to genotyping results. This study was registered by the French National Agency for Medicine and Health Products Safety and the Commission Nationale de l'Informatique et des Libertés, was approved by the Ethics Committee of Paris-Boulogne, France, and conformed to international ethical standards (ClinicalTrials.gov identifier: NCT00526383) [50].

Patients

Five hundred and sixty-nine in- or out-patients, aged 18–65 years, with a diagnosis of MDE in the context of MDD based on the Mini International Neuro psychiatric Interview, were included in these psychiatric settings [50]. Five hundred and twenty one (92%) patients were Caucasians, in other words, had two Caucasian parents. A minimum depression score of 18 on the 17-item Hamilton Depression Rating Scale (HAM-D) was required to ensure that patients qualified for MDE. To be included, patients required the initiation of a new antidepressant treatment. This clinical decision, the drug and its dose, were left to the treating psychiatrist, using 'real world' treatment options. Patients with DSM-IV-TR bipolar disorders, psychotic disorders, current substance abuse or dependence, pregnancy, breast feeding, organic brain syndromes or unstable medical conditions were excluded. Patients receiving anti psychotics or mood stabilizers before inclusion and/or for 4 months or more during the last year were excluded. All patients signed a written informed consent for study participation and for genetic analyses.

SNP selection & genotyping methods

Eight SNPs of NTRK2 were selected. Four were based on the results of Dong et al. [40], who showed their possible association with antidepressant efficacy in a sample of Mexican–American depressed patients: rs2289656, rs2289657, rs2289658 and rs56142442. And the other four were based on the results of the study of Perroud et al. [53], who evidenced their possible association with the outcome of suicidal ideation in depressed Caucasian patients treated with antidepressants: rs1187352, rs1439050, rs1778933 and rs3824519. These candidate SNPs were located on the NTRK2 gene (NTRK2 gene location: 87283417–

87641985 in GRCh37) (**Table 8**). To the best of our knowledge, there was no known functional variant in NTRK2.

SNP	Location and function	Position GRCh37	Major allele	Minor allele	MAF HapMap CEU	Available genotypes (n)	Homozygous for the major allele, n (%)	Heterozygous, n (%)	Homozygous for the minor allele, n (%)	χ^2	P-value
rs1439050	intron	87288192	G	T	33%	532	194 (36.4)	265 (49.8)	73 (13.7)	1.4	0.24
rs1187352	intron	87293456	G	A	36%	548	266 (48.5)	223 (40.7)	59 (10.8)	1.4	0.23
rs1778933	intron	87324410	T	C	35%	551	280 (50.8)	215 (39.0)	56 (10.1)	3.3	0.13
rs2289658	exon syn	87563369	A	G	4%	547	504 (92.1)	39 (7.1)	4 (0.7)	9.7	0.002*
rs2289657	intron	87563459	G	T	6%	553	514 (92.9)	37 (6.7)	2 (3.6)	2.2	0.14
rs2289656	intron	87563561	C	T	17%	547	340 (62.2)	181 (33.1)	26 (4.8)	0.09	0.76
rs3824519	intron	87570003	C	T	8%	552	468 (84.8)	75 (13.6)	9 (1.6)	7.86	0.005*
rs56142442	exon syn	87636264	C	T	–	553	551 (99.6)	2 (0.4)	0	0.002	0.96

Table 8 : Allelic repartition of eight NTRK2 genetic polymorphisms and Hardy–Weinberg equilibrium in our sample of depressed patient

*Significant deviation from Hardy–Weinberg equilibrium. MAF: Minor allele frequency; n: Number of patients.

Genomic DNA was extracted from circulating blood leukocytes by Gentra® Puregene® Blood Kits, following the manufacturer’s protocol (Qiagen, MN, USA) and stored at -20°C. The genotyping was performed by the IntegraGen company (Evry, France) using the Fluidigm® BioMark™ HD system (Fluidigm Corporation, CA, USA). Some genetic results were not available depending on each SNP, ranging from 16 to 37 patients, due to a lack of amplification and low call rates (**Table 8**). All SNPs had a call rate >97%, except rs2289658 (96.5%) and rs1439050 (94%). To identify linkage disequilibrium between SNPs, a haplotype analysis was performed with THESIAS 3.1 [181]. Moderate linkage disequilibrium was defined by D’ criteria absolute value between 0.50 and 0.75. High linkage disequilibrium was defined by D’ criteria absolute value between 0.75 and 1.

Antidepressants

An antidepressant monotherapy was chosen by the psychiatrist, using ‘real world’ treatment options. The antidepressant medication belonged to one of four antidepressant classes (SSRI, SNRI, tricyclics and others). SSRI (n = 220) and SNRI (n = 220) were the two most prescribed antidepressant drug classes.

Concomitant treatments

Antipsychotics, mood stabilizers and stimulants were not permitted during the study. Benzodiazepines, at the minimum effective dose and for the minimum time period, were allowed as well as psychotherapies.

Antidepressant efficacy

The HAMD scale [81] was rated by trained clinicians at baseline, followed by 1 month, 3 months and 6 months after the beginning of antidepressant treatment.

HAMD total scores, response and remission rates were assessed after 1, 3 and 6 months of antidepressant treatment. The response rate was defined by a decrease of the HAMD total score of at least 50% from baseline to follow-up [52]. The remission rate was defined by a HAMD total score of 7 or less at follow-up [52] and was the primary end point.

Statistical analysis

Statistical analyses were performed with the R 3.2.2 software. After testing the Hardy–Weinberg equilibrium using χ^2 tests, each SNP was studied in three groups (two homozygote and one heterozygote groups) and in two groups (the heterozygote group being associated with one of the homozygote groups to test dominant and recessive models).

Both ‘intent to treat’ (main analyses) and ‘last observation carried forward’ methods were applied. All the time points were analyzed (baseline, 1, 3 and 6 months).

Due to the number of SNPs studied and to take into account the increased risk of false-positive results due to the high number of comparisons. Bonferroni’s corrections were applied, the threshold for significance being $0.05/8 = 0.00625$. For the primary objective, intergenotypic comparisons were computed using χ^2 for response and remission rates and ANOVAs for repeated measures for the HAMD total score. If the number of patients in any group was below 20, non-parametric Kruskal–Wallis and Wilcoxon tests were computed. Multivariate analyses (i.e., logistic regressions for response and remission and linear regressions for HAMD total score) were performed to control for potential confounders among demographic and clinical variables. Indeed, covariables of the multivariate models were selected on the basis of a significant association ($p < 0.05$) with at least one SNP at baseline. For the secondary objective, the primary analysis was performed in a subgroup of Caucasian patients.

The a priori power estimation, which took into account the estimated attrition rate (40% at 3 months and 60% at 6 months) was performed with G*Power 3.1.9.2. The power to detect a 10% response/remission difference between two groups of genotypes, with an alpha risk of 5%, was 93% at 3 months and 79% at 6 months.

3.3.12 Results

Sample characteristics

The 569 patients were mainly women (69.6%). Their mean age was 46.2 years (standard deviation = 13.2). Their mean HAMD score at baseline was 24.6 (standard deviation = 5.0). Of these patients, 86.8% were hospitalized at baseline and 74.8% had a recurrent MDD. Five hundred and twenty one (92%) patients were Caucasian, in other words, had two Caucasian parents.

Patients who prematurely dropped out from the study (123 [21.6%] patients after 1 month, 246 [42.2%] after 3 months and 328 [57.6%] after 6 months) did not significantly differ from completers for age, sex, HAMD score at baseline, presence of recurrent MDEs, antidepressant treatment classes and allelic frequencies of the eight NTRK2 polymorphisms. The dropout reasons were: discontinuation of the antidepressant medication studied (30.1%), prescription of unauthorized drugs (9.9%), change of diagnosis not compatible with the study (5.3%), patient's decision (5.8%), lost during follow-up (41.1%), and others (7.8%). **Table 8** shows the allelic repartition of the eight NTRK2 SNPs. Since there were no homozygous patients for the minor allele and only two heterozygous patients for the rs56142442, this SNP was not analyzed. There was a deviation from the Hardy–Weinberg equilibrium for two other SNPs (rs2289658 and rs3824519). The haplotype analysis (**Supplementary Table S4**) showed that rs1439050, rs1187352 and rs1778933 were in moderate linkage disequilibrium and that rs2289658, rs2289657, rs2289656 and rs3824519 were in high linkage disequilibrium. The demographic and clinical features of the cohort according to each SNP are described in **Table 9**. The genotype groups (analyzed either in three or in two groups) did not significantly differ for these demographic and clinical features, neither in the whole sample and Caucasian patients.

Outcome of depression after antidepressant treatment

In the whole sample, the intent to treat analysis showed that three out of eight SNPs, in other words, rs1187352, rs1439050 and rs3824519 were associated with at least one efficacy

outcome in bivariate analyses ($p < 0.05$). Rs1187352 was associated with remission rates after 1 month, rs1439050 with the HAMD total score decreasing after 3 months, and rs3824519 with the remission rates after 6 months (**Table 10**). However, these associations were not statistically significant after Bonferroni's corrections, and after multivariate analyses controlling for age, sex, educational level and previous antidepressant treatment. Accordingly, the last observation carried forward analyses confirmed previous results. Additionally, the analysis of completers using an ANOVA for repeated measures, confirmed previous results. A posteriori statistical power estimations, taking attrition into account, were performed for the bivariate tests which had a p -value < 0.05 . The power estimations evidenced a 99.9% power for rs1187352 based on the remission rate after one month, a 93.5% power for rs3824519 based on remission rates after 6 months and a 63% power for rs1439050 based on the HAMD total score after 3 months. In the subgroup of Caucasian patients, no significant association was observed between the eight NTRK2 polymorphisms and outcome of depression after antidepressant treatment.

	rs1439050			rs1187352			rs1778933			rs2289658			rs2289657			rs2289656			rs3824519		
Genotype	GG	GT	TT	GG	GA	AA	TT	TC	CC	AA	AG	GG	GG	GT	TT	CC	CT	TT	CC	CT	TT
Patients (n)	194	265	73	266	223	59	280	215	56	504	39	4	514	37	2	340	181	26	468	75	9
Caucasian patients (n)	190	236	60	243	204	56	252	196	55	467	31	2	475	29	2	307	169	25	432	65	8
Age (m(sd))	45 (13.3)	46.5 (13.1)	49 (13.0)	45.7 (12.8)	46.4 (13.6)	47.9 (12.6)	45.7 (12.7)	47.4 (13.5)	44.7 (13)	46.2 (13.3)	45.6 (11.3)	58.1 (1.7)	46.2 (13.2)	47.3 (11.2)	59.5 (0.3)	45.1 (13.6)	48.3 (12.0)	47.9 (12.2)	46.4 (13.3)	45.3 (11.5)	47.2 (14.2)
Women (%)	71.6	69.4	68.5	69.9	71.7	64.4	68.6	72.6	69.6	71.4	59	50	70.6	62.2	0	69.7	69.1	84.6	70.3	68	55.6
Recurrent MDD (%)	76.2	74	75.3	73.6	75.3	81.4	71.7	78.1	78.6	75.5	74.4	50	75	73	100	77.1	70	84.6	74.7	76	77.8
High educational level (%)	53.1 [†]	36.4 [†]	47.9 [†]	47.2 [‡]	37.7 [‡]	61 [‡]	57.1	39.1	46.2	44.3	53.8	0	44.4	51.4	0	48.1	39.8	30.8	43.9	49.3	11.1
HAMD-17 (m(sd))	24.2 (5.0)	24.6 (4.7)	24.9 (5.3)	24.3 (4.8)	24.7 (5.0)	25 (4.8)	24.6 (5.0)	24.3 (4.8)	25 (4.9)	24.5 (4.9)	25.1 (5.5)	23 (3.6)	24.5 (4.9)	24.7 (5.7)	26 (1.4)	24.5 (5.1)	24.4 (4.8)	24.8 (3.3)	24.5 (4.8)	24.2 (5.7)	25.8 (3.6)
Previous antidepressant treatment (%)	77.7	79.6	76.7	74.7	83.4	78	74.6	84.2	76.8	79.1	71.8	100	78.6	78.4	100	77.1	80	88.5	78.6	80	77.8
Current Antidepressant :																					
SSRI (%)	40	39	38	41	39	27	40	38	38	39	49	25	39	46	0	40	37	46	38	41	44
SNRI (%)	36	40	38	39	36	44	39	38	41	38	36	50	38	41	50	38	40	31	39	36	22
Others (%)	24	21	24	20	25	29	21	24	21	23	15	25	23	13	50	22	23	23	23	23	34

Table 9 : Demographic and clinical features at baseline according to the NTRK2 genetic polymorphisms studied.

[†] $p = 0.001$ (bivariate analysis) for intergenotypic comparisons (three groups). [‡] $p = 0.003$ (bivariate analysis) for intergenotypic comparisons (three groups). HAMD-17: Hamilton Depression Rating Scale 17 items at baseline; MDD: Major depressive disorder; m: Mean; SNRI: Serotonin and norepinephrine reuptake inhibitor; SSRI: Selective serotonin reuptake inhibitor.

	rs1439050			rs1187352			rs1778933			rs2289658			rs2289657			rs2289656			rs3824519		
Genotype	GG	GT	TT	GG	GA	AA	TT	TC	CC	AA	AG	GG	GG	GT	TT	CC	CT	TT	CC	CT	TT
After 1 month of treatment																					
Attrition (%)	17.5	23.8	19.2	20.3	22	22	19.3	22.8	25	21.2	20.5	0	21.6	18.9	0	21.2	21.5	19.2	20.9	22.7	11.1
HAMD-17 (m (sd))	13.7 (6.7)	14.8 (6.6)	15.3 (7.2)	14.2 (7.1)	15 (6.7)	13.5 (6.9)	14.7 (7.0)	14.3 (6.5)	14.1 (7.9)	14.4 (6.8)	16 (7.5)	11.8 (6.7)	14.4 (6.9)	15.9 (7.6)	8 (8.5)	14.8 (7.1)	14.4 (6.7)	11.8 (4.4)	14.3 (6.8)	14.9 (6.5)	11.5 (10.4)
Response (%)	42.5	38.1	33.9	40.6	37.9	41.3	39.4	38.6	40.5	40.3	25.8	25	40.4	23.3	50	37.7	40.1	47.6	40.5	34.5	50
Remission (%)	21.9	15.3	15.3	22.6*	12.1*	26.1*	19	15.1	26.2	18.6	16.1	25	18.9	16.7	50	18.3	17.6	23.8	19.2	13.8	50
After 3 months of treatment**																					
Attrition (%)	40.2	44.2	47.9	41	46.2	44.1	41.8	46	41.1	42.5	61.5	0	42.4	59.5	0	45.9	41.4	26.9	42.9	46.7	33.3
HAMD-17 (m (sd))	11.3 [†] (6.5)	13.6 [†] (7.9)	11.7 [†] (8.4)	12.6 (7.3)	12.9 (8.0)	11.5 (7.9)	13 (7.8)	12.3 (7.2)	11.8 (8.4)	12.7 (7.6)	10.5 (7.8)	11.5 (6.8)	12.8 (7.6)	10.3 (7.0)	8.5 (6.4)	12.4 (7.3)	12.6 (8.0)	15.9 (8.0)	12.8 (7.7)	11.2 (7.1)	12 (4.3)
Response (%)	55.2	50	60.5	49.7	55.8	54.5	49.7	56	57.6	51.7	66.7	75	51.4	66.7	100	52.7	56.6	26.3	51.7	60	50
Remission (%)	30.2	25.7	31.6	26.1	26.7	42.4	27	25.9	39.4	26.9	46.7	25	26.7	40	50	26.6	31.3	15.8	27	35	16.7
After 6 months of treatment																					
Attrition (%)	53.1	59.2	60.3	54.5	60.5	57.6	56.8	56.3	62.5	56.9	66.7	25	57.2	64.9	0	57.9	56.9	53.8	57.9	56	44.4
HAMD-17 (m (sd))	10.1 (8.1)	11.5 (7.8)	10.2 (7.2)	10.5 (8.1)	10.7 (7.4)	12.5 (8.6)	10.8 (8.2)	10.6 (7.0)	12.3 (9.6)	10.8 (7.9)	10.2 (7.7)	16.3 (10.5)	10.8 (7.9)	11.3 (7.5)	16.5 (14.8)	11.1 (8.0)	10.6 (7.7)	10.9 (8.5)	10.5 (7.9)	12.6 (7.3)	13 (9.4)
Response (%)	65.9	63.9	69	62.8	71.6	60	63.6	70.2	57.1	65	76.9	33.3	65.5	69.2	50	66.4	62.8	66.7	66.5	57.6	60
Remission (%)	47.3	37	41.4	42.1	43.2	36	41.3	42.6	38.1	41.9	30.8	33.3	42.3	23.1	50	42	39.7	41.7	44.7 [§]	21.2 [§]	40 [§]

Table 10 : Antidepressant efficacy after 1, 3 and 6 months of treatment, according to the NTRK2 genetic polymorphisms studied.

† p = 0.038 (bivariate analysis) for inter-genotypic comparisons (three groups).

‡ p = 0.012 (bivariate analysis) for inter-genotypic comparisons (three groups).

§ p = 0.04 (bivariate analysis) for inter-genotypic comparisons (three groups).

HAMD-17: Hamilton Depression Rating Scale 17 items; m: Mean

3.3.13 Discussion

This study fails to show an association between the eight NTRK2 SNPs selected (rs1187352, rs1439050, rs1778933, rs2289656, rs2289657, rs2289658, rs3824519 and rs56142442) and the response and remission rates after antidepressant treatment in depressed patients. Our results confirm, in a greater sample, those of Dong et al. [40] for rs2289656, rs2289657, rs2289658 and rs56142442. They also confirm, with a greater follow-up duration, those of Hennings et al. [41] for rs1439050, rs1778933, rs2289656 and rs3824519.

Regarding the four NTRK2 genetic polymorphisms which were previously associated with suicidal ideation in depressed Caucasian patients treated with antidepressants (rs1187352, rs1439050, rs1778933 and rs3824519) [53], we fail to show their association with response and remission rates of depression post treatment. This difference could be explained by the number of symptoms taken into account for the definition of response/remission as compared with suicidal ideation assessed alone. Of note, to the best of our knowledge, there are no published data beyond major depression, in other psychiatric or non-psychiatric disorders, and with other drug treatments, showing a relevance of the assessment of some NTRK2 SNPs to predict treatment response.

Results of the haplotype analyses, showing that rs1439050, rs1187352 and rs1778933 were in linkage disequilibrium, are in line with those of Perroud et al. [53] in Caucasians. Indeed, they reported a linkage disequilibrium for rs1187352 and rs1778933 in a same haplotype bloc. We also show a high linkage disequilibrium for rs2289658, rs2289657, rs2289656 and rs3824519, which is in line with the results of Dong et al. [40] in Mexican– American. They report that rs2289657, rs2289656 and rs3824519 were in linkage disequilibrium and determined a haplotype bloc.

The main strengths of this study are its large sample size, its long-term follow-up (6 months), and a homogenous sample in terms of diagnosis (MDD patients only), with a majority of Caucasian patients and an analysis of the Caucasian subgroup. Nevertheless, this study has some limitations. It is a no randomized naturalistic open study, the treatment being chosen by the psychiatrist according to his clinical assessment and own experience. The first limit of this study is the high attrition rate (42.2% after 3 months and 57.6% after 6 months), although similar to the one of other cohorts of MDD patients such as the STAR*D cohort [96]. In this study, comorbid anxiety, hormonal changes, life events or low income were not specifically assessed. However, they may predict antidepressant response. Thus, their potential associations with the NTRK2 SNPs or potential confounding effects on outcome were not

tested. Moreover, the study is underpowered to draw firm conclusions regarding the genetic effect of this gene. In addition, for the NTRK2 gene, the approach based on candidate SNPs is limited by the poor rationale to identify candidate SNPs since their functionality is unknown. Finally, since NTRK2 is involved in the mechanisms of action of antidepressant drugs [26], new studies could be useful in this field. Beyond powerful genome-wide association studies, searching for rare variants in the NTRK2 gene may also be a promising strategy.

3.3.14 Conclusion

Despite its moderate power, this study in depressed patients fails to show an impact of eight NTRK2 SNPs on response and remission after 6 months of antidepressant treatment, suggesting that there is no benefit to genotype these NTRK2 SNPs in daily practice to predict outcomes after antidepressant treatment in depressed patients.

3.4 INTERACTION ENTRE LES POLYMORPHISMES DU TRKB ET LES CARACTERISTIQUES CLINIQUES DE LA DEPRESSION SUR LA REPONSE APRES TRAITEMENT ANTIDEPRESSEUR

Cette partie est l'étude de l'influence des 8 polymorphismes du TRKB associés aux 5 caractéristiques cliniques du TDU sur la réponse après traitement antidépresseur. Avant d'étudier l'influence de ces interactions sur la réponse après traitement antidépresseur, nous avons étudié au préalable l'influence des caractéristiques cliniques sur la réponse après traitement antidépresseur. Ce travail préalable fait l'objet d'un article en cours d'écriture.

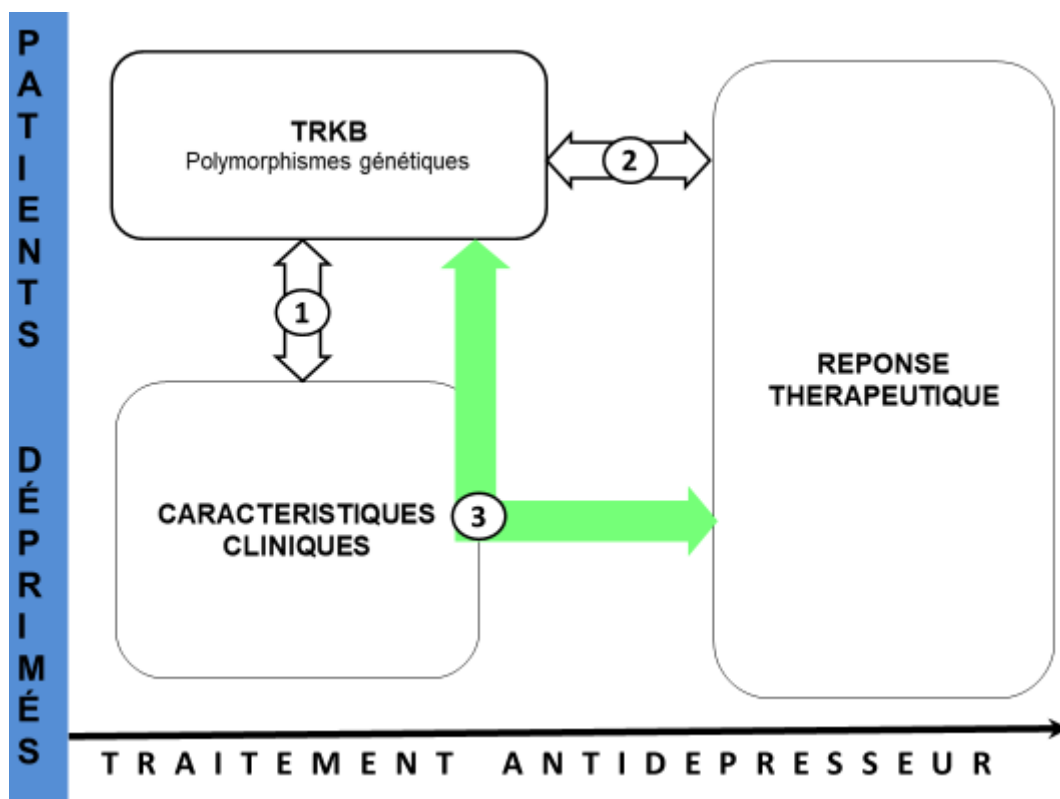


Figure 7 : Etape 3 de la thèse

Légendes ; TRKB : Récepteur Tyrosine-Kinase B

3.4.1 Introduction

Certaines caractéristiques cliniques du TDU sembleraient influencer la réponse au traitement : la sévérité de l'EDC, les antécédents de prise d'antidépresseur, les antécédents de tentative de suicide et les antécédents de dépression. La sévérité de l'EDC est un bon prédicteur d'une réponse aux traitements, les patients les plus sévères ont une moins bonne rémission après traitement par antidépresseur [16-22]. Paradoxalement, ils auraient une meilleure amélioration de la sévérité [182]. Cela s'expliquerait par le fait que les antidépresseurs auraient une meilleure efficacité chez les patients ayant une dépression sévère [16] sans pour autant permettre la rémission. Les antécédents de prise d'antidépresseur [20,183], de dépression [184,185] et de tentative de suicide (TS) [186] sembleraient être associés avec une plus mauvaise réponse.

Nous n'avons pas trouvé, dans notre étude, de lien significatif entre les polymorphismes du TRKB et la réponse thérapeutique. Cependant, selon notre étude, un polymorphisme du TRKB (rs2289656) aurait une influence sur l'une des caractéristiques cliniques de l'EDC (antécédent de TS récente) et ces dernières l'auraient sur la réponse après traitement antidépresseur [16-22,183-186]. Ces polymorphismes associés à certaines caractéristiques cliniques de l'EDC pourraient avoir un impact sur cette réponse.

Nous avons donc pour objectif d'explorer les interactions entre des polymorphismes du TRKB et des caractéristiques cliniques de la dépression sur la réponse thérapeutique après traitement antidépresseur : c'est-à-dire l'effet modulateur des polymorphismes génétiques sur l'association entre des caractéristiques cliniques du TDU et la réponse thérapeutique.

3.4.2 Méthode

3.4.2.1 Critères d'inclusion et choix des variables

La description des critères d'inclusions, des évaluations génétiques, des caractéristiques cliniques de l'EDC, et de l'évaluation de la réponse thérapeutique sont décrits dans la partie « METHODE » de ce travail.

3.4.2.2 Analyse statistique

Nous avons étudié l'influence des polymorphismes et des caractéristiques cliniques séparément sur la réponse après traitement antidépresseur. Cela revient à effectuer un modèle par exemple pour le calcul de la sévérité (HAMD-17):

$$\text{Score HAMD-17} = \sum \alpha_i * (\text{caractéristiques cliniques}) + \sum \beta_i * \text{SNP} + \delta$$

Nous nous intéressons à l'interaction entre les caractéristiques cliniques et les SNP du TRKB. Cela permet de savoir si le polymorphisme génétique peut avoir une influence sur la réponse dans une sous population avec certaines caractéristiques cliniques. Ce qui revient mathématiquement à rechercher les coefficients γ_i du modèle suivant :

$$\text{Score HAMD-17} = \sum \alpha_i * (\text{caractéristiques cliniques}) + \sum \beta_i * \text{SNP} + \sum \gamma_i * (\text{caractéristiques cliniques}) * \text{SNP} + \delta'$$

Pour des variables qualitatives telles que la rémission, le modèle est le suivant :

$$\text{Log} \left(\frac{\text{probabilité (rémission)}}{1 - \text{probabilité (rémission)}} \right) = \sum \alpha_i * (\text{caractéristiques cliniques}) + \sum \beta_i * \text{SNP} + \sum \gamma_i * (\text{caractéristiques cliniques}) * \text{SNP} + \delta'$$

Dans une première étape, nous avons analysé les associations entre les caractéristiques cliniques du TDU (la sévérité à l'inclusion et les antécédents de prise d'antidépresseur, de dépression et de TS récentes et anciennes) et la réponse thérapeutique (l'amélioration de l'HAMD-17, la réponse et la rémission).

Des analyses bivariées ont été réalisées : tests t de Student, U de Mann Whitney et H de Kruskal-Wallis pour les variables quantitatives et tests de Chi-2 pour les variables qualitatives. Des corrélations de Spearman ont été utilisées pour évaluer les liens entre 2 variables quantitatives. Des tests paramétriques ont été utilisés quand la distribution suivait une loi normale et que le nombre de sujets dans chacun des échantillons comparés était supérieur à 20, des tests non-paramétriques dans les autres cas.

Les analyses multivariées ont été réalisées à l'aide de régression linéaire pour les variables quantitatives et de régression linéaire généralisée pour les variables qualitatives. Nous avons ajusté chaque caractéristique clinique testée sur à la fois les caractéristiques sociodémographiques ayant une différence significative entre les groupes et sur les autres caractéristiques cliniques. Nous n'avons cependant pas ajusté les TS récentes et TS anciennes entre elles car ces 2 variables sont très associées. Les variables

sociodémographiques associées significativement aux polymorphismes génétiques de TRKB (l'âge, le niveau d'études et le sexe) étaient ajoutées dans le modèle multivarié.

Un seuil de significativité de Bonferroni de 0.01 est retenu car 5 caractéristiques cliniques sont évaluées (0.05/5).

La deuxième étape analyse l'effet du terme d'interaction entre caractéristiques cliniques et polymorphisme génétiques (caractéristiques cliniques * SNP) sur la réponse (l'amélioration de l'HAMD-17, la réponse et la rémission). Nous avons analysé les polymorphismes en 2 groupes afin d'augmenter la puissance d'autant plus que l'effet d'un hétérozygote seul différent des 2 homozygotes est biologiquement peu crédible.

Les analyses sont réalisées avec des régressions linéaires pour l'amélioration de l'HAMD-17 et des régressions logistiques pour la réponse et la rémission. Des analyses sont ajustées sur les variables sociodémographiques associées en bivarié au SNP du TRKB (l'âge, le niveau d'étude et le sexe) ainsi que sur les autres caractéristiques cliniques.

Un seuil de significativité de 0.00125 est retenu pour prendre en compte l'analyse sur 8 SNP et 5 caractéristiques (0.05/(8x5)).

3.4.3 Résultats

3.4.3.1 Description de la population

La population a été décrite précédemment.

3.4.3.2 Caractéristiques cliniques et réponse après traitement antidépresseur

Sévérité

Nous observons que les patients avec une plus grande sévérité (HAMD-17) sont significativement moins en rémission à 1, 3 et 6 mois de traitement antidépresseur avec des p respectif de 0.006, 0.0004 et 0.004 ajusté sur l'âge, le niveau d'étude, le sexe, les antécédents de TS récentes, d'EDC et d'antidépresseur. Plus l'HAMD-17 initial est élevé, plus, d'une part, l'HAMD-17 à 1, 3 et 6 mois est significativement élevé (avec un p ajusté à respectivement $6 \cdot 10^{-10}$, $3 \cdot 10^{-7}$ et 10^{-4}) et plus, d'autre part, l'amélioration de l'HAMD-17 à 1, 3 et 6 mois de

traitement antidépresseur est significativement importante (avec un estimate respectif à 0.59, 0.6 et 0.64, p ajusté <0.00000001).

TS

Après ajustement sur l'âge, le niveau d'études, le sexe, l'HAMD-17, les antécédents d'EDC et d'antidépresseur, un antécédent de TS récente est associé à une meilleure efficacité des antidépresseurs : Les patients avec une TS récente ont significativement 3 fois plus de réponse (après ajustement, 3.2 CI 95:[1.52 - 7.31], $p=0.003$) et 2.2 fois plus de rémission (après ajustement, 2.77 CI 95:[1.45 - 5.42]) après 6 mois de traitement antidépresseur. Ces patients ont une amélioration significativement plus importante de leur sévérité à HAMD-17 (OR=3.63 [1.63 - 5.63], $p=0.0004$ à M3 et OR=4.3 [1.9 - 6.7], $p=0.0005$ à M6 de traitement antidépresseur. Il persiste une tendance après ajustement ($p=0.013$ et 0.011).

Nous ne trouvons pas de lien significatif entre les TS anciennes et l'efficacité des traitements antidépresseurs.

Antécédents d'EDC et d'antidépresseur

Les antécédents d'EDC et d'antidépresseur sont associés significativement à une moindre réponse après antidépresseurs à 3 mois (avec respectivement un OR = 0.51 et 0.48 et $p=0.007$ et 0.006). Les antécédents d'antidépresseur sont aussi associés significativement à une moindre amélioration de la note de l'HAMD-17 après traitement antidépresseur. Ces résultats ne sont plus significatifs après ajustement.

	Réponse (OR [IC])	p	p ajust	Rémission (OR [IC])	p	p ajust	HDRS (estimate [IC])	rho	p	p ajust
HDRS M0										
M1	1.02 [0.98 - 1.06]	0.33	0.43	0.93 [0.88 - 0.98]	0.0053	0.00	0.41 [0.28 - 0.53]	0.28	7 10 ⁻¹⁰ +	6 10 ⁻¹⁰ +
M3	1.02 [0.98 - 1.07]	0.4	0.59	0.92 [0.87 - 0.97]	0.001+	0.0004+	0.41 [0.25 - 0.58]	0.24	7 10 ⁻⁶ +	3 10 ⁻⁷ +
M6	1.02 [0.96 - 1.07]	0.59	0.99	0.94 [0.89 - 0.99]	0.025+	0.004+	0.36 [0.16 - 0.55]	0.21	10 ⁻³ +	10 ⁻⁴ +
TS récente										
M1	1.23 [0.79 - 1.91]	0.35	0.39	0.93 [0.52 - 1.6]	0.8	0.83	0.23 [-1.29 - 1.76]	N/A	0.76	0.54
M3	1.68 [0.996 - 2.88]	0.053	0.084	1.42 [0.8 - 2.47]	0.22	0.077	-1.59 [-3.56 - 0.37]	N/A	0.11	0.013
M6	3.01 [1.48 - 6.65]	0.003+	0.003+	2.19 [1.2 - 4.02]	0.001+	0.0023+	-1.94 [-4.26 - 0.39]	N/A	0.1	0.011
TS ancienne										
M1	0.95 [0.63 - 1.42]	0.8	0.92	0.72 [0.42 - 1.21]	0.22	0.35	0.52 [-0.86 - 1.9]	N/A	0.46	0.51
M3	0.68 [0.42 - 1.08]	0.11	0.19	0.82 [0.47 - 1.4]	0.48	0.44	1.54 [-0.25 - 3.3]	N/A	0.091	0.085
M6	0.72 [0.41 - 1.28]	0.26	0.05	0.75 [0.42 - 1.3]	0.3	0.027	1.76 [-0.38 - 3.9]	N/A	0.11	0.018
ATCD_EDC										
M1	0.72 [0.47 - 1.09]	0.12	0.32	0.61 [0.37 - 1.01]	0.047	0.19	1.25 [-0.19 - 2.7]	N/A	0.089	0.088
M3	0.51 [0.31 - 0.83]	0.007+	0.083	0.68 [0.40 - 1.15]	0.15	0.87	2.59 [0.78 - 4.41]	N/A	0.0052	0.15
M6	0.75 [0.4 - 1.36]	0.35	0.77	0.93 [0.53 - 1.65]	0.8	0.66	1.39 [-0.8 - 3.59]	N/A	0.21	0.62
ATCD_ANTIDEP										
M1	0.69 [0.45 - 1.07]	0.098	0.3	0.75 [0.45 - 1.31]	0.3	0.68	-0.14 [-1.67 - 1.39]	N/A	0.86	0.77
M3	0.48 [0.27 - 0.81]	0.006+	0.16	0.55 [0.32 - 0.97]	0.035	0.076	1.89 [-0.075 - 3.85]	N/A	0.059	0.24
M6	0.64 [0.31 - 1.23]	0.19	0.59	0.74 [0.4 - 1.37]	0.33	0.31	0.95 [-1.44 - 3.34]	N/A	0.44	0.73

Tableau 11 : Influence des caractéristiques cliniques sur la réponse, rémission et HDRS après traitement antidépresseur

Légende: réponse, rémission : réponse, rémission sous traitement antidépresseur ; HDRS : échelle de Hamilton ; HDRS_M0 : HDRS à l'inclusion ; ATCD_EDC, ATCD_ANTIDEP : antécédents d'épisode dépressif caractérisé, d'antidépresseur ; TS tentative de suicide ; TS récente (<1 mois) ; TS ancienne (>1mois) ; M1, M2, M3 évaluation à 1, 3 et 6 mois.

+ : lien significatif (p<0.01)

3.4.3.3 Interactions

En prenant en compte le seuil de Bonferroni de 0.00125, nous trouvons 2 interactions significatives : le rs3824519, en groupant l'homozygote le plus fréquent avec l'hétérozygote, est en interaction significative avec les antécédents d'EDC et d'antidépresseur pour l'HAMD-17 à 1 mois avec un p respectivement à 0.0004 et 0.0008 (**tableau 12 et 13**).

Pour ce SNP, il n'y a que 9 patients homozygotes de l'allèle le moins fréquent et seulement 6 encore présents dans l'étude à 1 mois. Nous pouvons donc penser que ces résultats sont dus au hasard de l'échantillonnage, d'autant que nous ne trouvons aucun lien significatif aux autres temps et pour les autres variables de l'efficacité du traitement antidépresseur (rémission et réponse).

	rs1439050			rs1187352			rs1778933			rs2289658			rs2289657			rs2289656			rs3824519		
	rep	rem	hdrs	rep	rem	Hdrs	rep	rem	hdrs	rep	rem	hdrs	rep	rem	hdrs	rep	rem	hdrs	rep	rem	hdrs
HDRS M0																					
M1	0.844	0.071	0.694	0.381	0.057	0.089	0.352	0.051	0.2	0.889	0.97	0.456	0.972	0.883	0.468	0.355	0.899	0.207	0.868	0.752	0.258
M3	0.082	0.025	0.007	0.233	0.103	0.044	0.278	0.457	0.068	0.108	0.41	0.174	0.103	0.271	0.144	0.107	0.063	0.172	0.28	0.348	0.282
M6	0.874	0.111	0.357	0.451	0.691	0.617	0.915	0.222	0.719	0.201	0.663	0.487	0.177	0.521	0.427	0.381	0.516	0.738	0.277	0.767	0.41
ATCD EDC																					
M1	0.702	0.545	0.799	0.496	0.117	0.647	0.12	0.053	0.33	0.119	0.543	0.946	0.304	0.572	0.86	0.153	0.167	0.447	0.866	0.373	0.458
M3	0.374	0.42	0.933	0.473	0.177	0.97	0.924	0.785	0.592	0.455	0.685	0.947	0.681	0.356	0.629	0.483	0.407	0.443	0.992	0.364	0.377
M6	0.66	0.609	0.669	0.943	0.231	0.362	0.329	0.955	0.808	0.432	0.91	0.299	0.546	0.657	0.491	0.328	0.442	0.993	0.6	0.83	0.946
ATCD ANTIDEP																					
M1	0.627	0.584	0.774	0.18	0.187	0.271	0.505	0.159	0.855	0.103	0.056	0.36	0.133	0.027	0.337	0.304	0.185	0.066	0.128	0.095	0.454
M3	0.382	0.878	0.669	0.178	0.589	0.197	0.176	0.237	0.09	0.814	0.814	0.766	0.984	0.833	0.644	0.55	0.686	0.279	0.179	0.238	0.887
M6	0.875	0.737	0.971	0.985	0.792	0.943	0.983	0.726	0.268	0.988	0.779	0.113	0.983	0.77	0.227	0.332	0.324	0.533	0.829	0.267	0.599
TS récente																					
M1	0.576	0.34	0.868	0.987	0.523	0.288	0.693	0.429	0.966	0.792	0.583	0.501	0.776	0.635	0.538	0.303	0.564	0.402	0.246	0.419	0.099
M3	0.383	0.235	0.326	0.552	0.303	0.594	0.947	0.977	0.94	0.913	0.204	0.619	0.618	0.424	0.935	0.806	0.928	0.504	0.818	0.219	0.674
M6	0.223	0.021	0.146	0.121	0.033	0.093	0.087	0.262	0.34	0.984	0.333	0.437	0.987	0.985	0.711	0.535	0.358	0.407	0.219	0.826	0.455
TS ancienne																					
M1	0.825	0.968	0.48	0.68	0.431	0.82	0.3	0.584	0.629	0.169	0.556	0.844	0.186	0.489	0.797	0.958	0.669	0.572	0.337	0.166	0.137
M3	0.927	0.976	0.938	0.337	0.092	0.039	0.642	0.878	0.244	0.543	0.718	0.281	0.633	0.661	0.377	0.324	0.1	0.374	0.49	0.026	0.053
M6	0.209	0.031	0.3	0.199	0.07	0.114	0.802	0.996	0.849	0.343	0.422	0.466	0.292	0.26	0.332	0.382	0.801	0.763	0.055	0.01	0.024

Tableau 12 : Significativité (p) des interactions entre les polymorphismes du TRKB et les caractéristiques cliniques de la dépression sur la réponse, rémission et HDRS après traitement antidépresseur

Analyse en 2 groupes de polymorphisme en groupant l'hétérozygote avec homozygote de l'allèle le moins fréquent

Légende: rep, rem : réponse, rémission sous traitement antidépresseur ; HDRS : échelle de Hamilton ; HDRS_M0 : HDRS à l'inclusion ; ATCD_EDC, ATCD_ANTIDEP : antécédents d'épisode dépressif caractérisé, d'antidépresseur ; TS tentative de suicide ; TS récente (<1 mois) ; TS ancienne (>1mois) ; M1, M2, M3 évaluation à 1, 3 et 6 mois.

	rs1439050			rs1187352			rs1778933			rs2289658			rs2289657			rs2289656			rs3824519			
	rep	rem	hdrs	rep	Rem	hdrs	rep	rem	hdrs	rep	rem	hdrs	rep	rem	hdrs	rep	rem	hdrs	rep	rem	hdrs	
HDRS M0																						
M1	0.166	0.192	0.151	0.161	0.697	0.1	0.964	0.641	0.573	0.539	0.411	0.264	0.981	0.981	0.234	0.378	0.831	0.533	0.294	0.521	0.413	
M3	0.11	0.115	0.098	0.642	0.192	0.742	0.344	0.642	0.352	0.987	0.37	0.363	1	0.981	0.434	0.545	0.556	0.921	0.555	0.8	0.943	
M6	0.411	0.566	0.469	0.078	0.662	0.032	0.373	0.608	0.187	0.987	0.987	0.478	0.988	0.988	0.046	0.373	0.394	0.304	0.263	0.726	0.706	
ATCD EDC																						
M1	0.146	0.022	0.627	0.027	0.026	0.208	0.806	0.205	0.355	0.981	0.981	0.174	NA	NA	NA	0.419	0.431	0.651	0.979	0.986	0.0004*	
M3	0.275	0.638	0.721	0.386	0.607	0.76	0.93	0.883	0.534	0.981	0.981	0.258	NA	NA	NA	0.593	0.814	0.797	0.987	0.988	0.643	
M6	0.624	0.502	0.591	0.157	0.557	0.552	0.761	0.36	0.836	0.987	0.987	0.932	NA	NA	NA	0.988	0.801	0.394	NA	NA	NA	
ATCD ANTIDEP																						
M1	0.076	0.182	0.151	0.029	0.009	0.1	0.188	0.017	0.077	NA	NA	NA	NA	NA	NA	0.809	0.17	0.495	0.978	0.986	0.0008*	
M3	0.183	0.18	0.019	0.324	0.695	0.228	0.77	0.622	0.284	NA	NA	NA	NA	NA	NA	0.75	0.694	0.671	0.987	0.987	0.694	
M6	0.653	0.845	0.568	0.666	0.632	0.186	0.705	0.354	0.367	NA	NA	NA	NA	NA	NA	0.989	0.919	0.343	NA	NA	NA	
TS récente																						
M1	0.344	0.646	0.536	0.16	0.531	0.098	0.13	0.113	0.044	NA	NA	NA	NA	NA	NA	0.979	0.988	0.264	0.844	0.969	0.684	
M3	0.51	0.919	0.365	0.69	0.131	0.45	0.656	0.342	0.347	NA	NA	NA	NA	NA	NA	0.987	0.988	0.392	0.986	0.988	0.714	
M6	0.088	0.008	0.023	0.533	0.024	0.571	0.22	0.019	0.3	NA	NA	NA	NA	NA	NA	0.988	0.987	0.343	0.988	0.987	0.372	
TS ancienne																						
M1	0.037	0.979	0.239	0.586	0.567	0.031	0.176	0.247	0.023	0.981	0.981	0.237	NA	NA	NA	0.44	0.949	0.925	0.912	0.774	0.191	
M3	0.779	0.883	0.225	0.688	0.99	0.632	0.508	0.757	0.632	0.981	0.981	0.319	NA	NA	NA	0.225	0.074	0.321	0.305	0.986	0.365	
M6	0.064	0.112	0.324	0.774	0.924	0.406	0.645	0.332	0.365	0.987	0.987	0.895	NA	NA	NA	0.988	0.987	0.021	0.579	0.987	0.708	

Tableau 13 : Significativité (p) des interactions entre les polymorphismes du TRKB et les caractéristiques cliniques de la dépression sur la réponse, rémission et HDRS après traitement antidépresseur

Analyse en 2 groupes de polymorphisme en groupant l'hétérozygote avec homozygote de l'allèle le plus fréquent

Légende: rep, rem : réponse, rémission sous traitement antidépresseur ; HDRS : échelle de Hamilton ; HDRS_M0 : HDRS à l'inclusion ; ATCD_EDC, ATCD_ANTIDEP : antécédents d'épisode dépressif caractérisé, d'antidépresseur ; TS tentative de suicide ; TS récente (<1 mois) ; TS ancienne (>1mois) ; M1, M2, M3 évaluation à 1, 3 et 6 mois. NA : non applicable par manque de patients homozygotes de l'allèle le moins fréquent ; * : Lien significatif (p<0.00125)

3.4.4 Discussion

3.4.4.1 Caractéristiques cliniques et réponse

Sévérité

Nous trouvons qu'une plus grande sévérité initiale est associée avec une plus grande diminution de celle-ci sous antidépresseur et une moins bonne rémission. Ceci est en accord avec la littérature antérieure [20]

TS

Nous trouvons que les patients avec un antécédent de TS récente ont significativement un meilleur taux de réponse et de rémission à 6 mois d'antidépresseurs. Les études de Lopez-Castroman et de Souery sembleraient indiquer un lien inverse chez les patients avec respectivement un antécédent de TS ou la présence d'un risque suicidaire [186,187] et la réponse thérapeutique. Notre étude est la seule à évaluer, de façon séparée, les TS récentes car l'évaluation des antécédents de TS anciennes ont une fiabilité discutable [188].

Par ailleurs, les comportements suicidaires sont associés à des modifications biologiques telles que l'inflammation et le système Gabaergique [189]. Nous retrouvons des modifications de l'inflammation chez les patients avec un EDC et une TS récente (i.e. reçus aux urgences pour TS) lorsque on les compare à ceux avec un EDC sans TS depuis au moins 1 an [190,191]. L'étude de Kim sur une population de 109 patients coréens semblerait montrer une augmentation de facteurs de l'inflammation (L'interleukine-2, l'interleukine 6 et l'interféron type 2) dans la dépression, mais une diminution relative de ces facteurs chez les patients avec une TS récente. L'étude de Haroon retrouve des résultats similaires sur une population américaine de 98 patients avec une dépression. Or certaines études montreraient que la présence d'inflammation dans la dépression induirait une plus grande résistance au traitement [190]. Cela semblerait indiquer l'importance de traiter rapidement les patients en dépression avec une TS récente.

Antécédent d'EDC et d'antidépresseur

Nous trouvons une moindre réponse à 3 mois de traitement antidépresseur chez les patients ayant un antécédent d'EDC ou un antécédent de traitement par antidépresseur, ce qui est similaire aux études sur le sujet [20,183-185]. Cette association ne tient pas après ajustement. Ceci est probablement dû d'une part à la puissance de l'étude et probablement au choix des variables d'ajustement qui sont corrélées : Les antécédents d'antidépresseur sont souvent associés à des antécédents d'EDC et inversement. L'ajustement croisé devrait, ainsi, diminuer l'impact de chacune des variables.

3.4.4.2 Interactions gènes-caractéristiques cliniques et réponse

Nous trouvons uniquement 2 interactions entre le rs3824519 et les antécédents d'antidépresseur et de dépression sur la sévérité au 1^{er} mois. Mais au vu du petit effectif d'un des 2 groupes et l'absence de résultat aux autres temps, ce résultat semble dû au hasard lié à l'échantillonnage. A notre connaissance, c'est la 2^e étude sur l'impact d'une association gène-caractéristiques cliniques de la dépression sur la réponse après traitement antidépresseur. Kautzky a associé plusieurs gènes avec des caractéristiques cliniques de la dépression [192]. L'association de polymorphismes de 3 gènes, dont le BDNF, la neurotrophine principale du récepteur TRKB, associé à la mélancolie aurait un impact sur la réponse dans les dépressions résistantes aux traitements. Cette étude évaluait un gène différent et des caractéristiques cliniques différentes à l'exception de la sévérité.

3.4.4.3 Limites de l'étude

Notre étude avait certaines limites. Elle ne prenait pas en compte certaines informations pouvant avoir un impact sur la réponse, telles que les événements de vie [193].

La force de notre étude est qu'elle s'appuie sur une grande cohorte homogène en matière de diagnostic avec une majorité de patients caucasiens. Le critère des TS récentes a une grande fiabilité car il est basé à la fois sur une auto-évaluation, une hétéro-évaluation et les dossiers médicaux. A notre connaissance, c'est la seule étude portant sur l'association entre TS récente et réponse après traitement antidépresseur. C'est aussi la première étude analysant les interactions du gène TRKB avec des caractéristiques cliniques sur cette réponse.

3.4.4.4 Perspectives

La littérature semblerait montrer des différences entre les TS récentes et les TS anciennes entre autres au niveau biologique [190,191]. Les TS récentes auraient un lien avec la réponse au traitement. Il serait intéressant de tester l'interaction d'autres gènes liés à l'inflammation avec ce critère clinique.

Dans notre étude, nous n'avons pas d'informations sur les événements de vie. Or certaines études sembleraient montrer une interaction avec certains gènes sur la réponse après traitement antidépresseur. Mandelli a trouvé qu'un stress de vie dans l'année précédant le 1^{er} épisode dépressif pourrait interagir avec les polymorphismes du gène 5-HTTLPR pour prédire la réponse après traitement antidépresseur [194]. Xu a trouvé aussi qu'un abus dans l'enfance

associé à certains gènes influencerait la réponse après traitement antidépresseur. Cette information aurait peut-être permis d'obtenir une association avec certains polymorphismes du TRKB [195].

3.4.5 Conclusion

Nous ne trouvons pas d'interactions entre les polymorphismes étudiés du TRKB et les caractéristiques cliniques de la dépression pouvant influencer la réponse après traitement antidépresseur.

Nous trouvons une influence des caractéristiques cliniques sur cette réponse.

Les patients avec un EDC plus sévère ont une amélioration de leur sévérité plus importante sous antidépresseur mais parviennent moins souvent à la rémission que les patients avec un EDC moins sévère.

Les patients avec des tentatives de suicide récentes ont une meilleure réponse et rémission aux antidépresseurs à 6 mois.

4 DISCUSSION

4.1 RAPPELS DES PRINCIPAUX RESULTATS

La **figure 8** présente les résultats de l'étude.

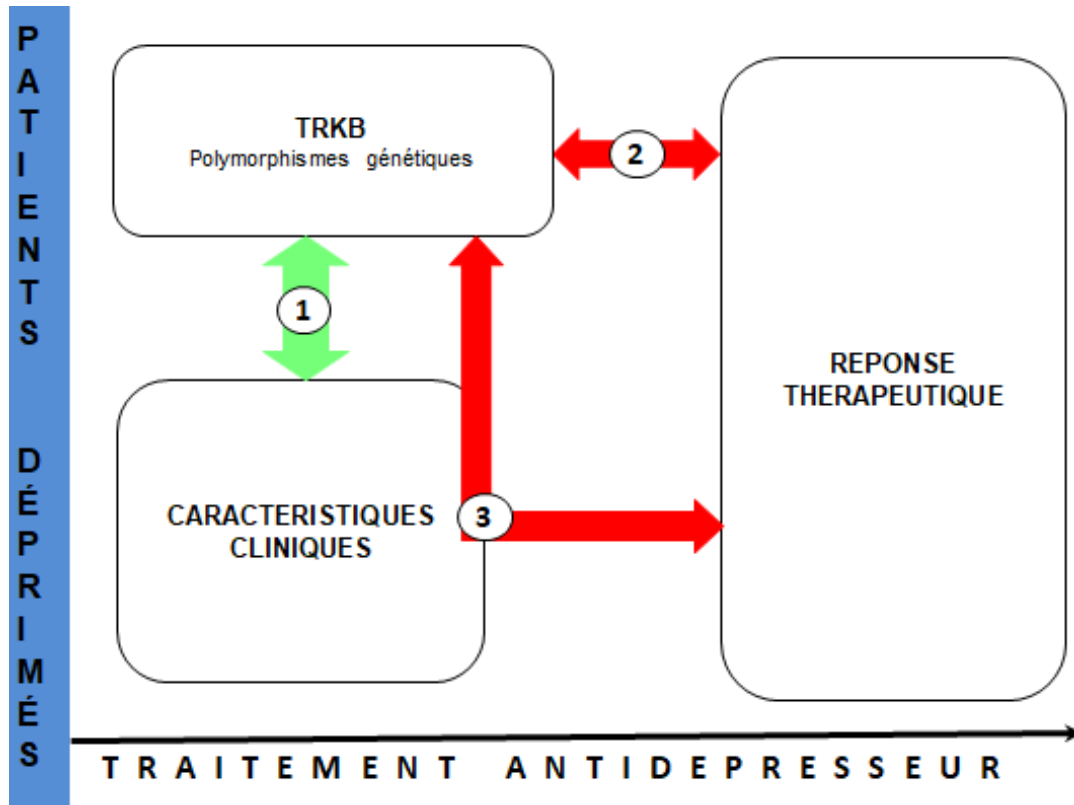


Figure 8 : Biomarqueurs et caractéristiques cliniques étudiés pour la réponse/rémission sous antidépresseurs : principaux résultats.

Nous avons étudié dans un premier temps l'association entre des polymorphismes du TRKB et des caractéristiques cliniques chez les patients avec un EDC. Nous avons trouvé un lien significatif entre le rs2289656 et les TS récentes. Les patients homozygotes CC ont 2.2 fois plus de TS récentes que les porteurs de l'allèle T.

Nous avons étudié ensuite l'association de ces polymorphismes avec la réponse après traitement par antidépresseurs. Premièrement, nous avons publié un article sur la revue de la littérature qui recensait 4 polymorphismes du TRKB dont 3 sur une population caucasienne (rs11140778, rs10868223, rs1659412) et un sur une population asiatique (rs1565445) associés avec la réponse thérapeutique après traitement par antidépresseurs. Deuxièmement, nous n'avons pas mis en évidence d'association entre les 8 polymorphismes génétiques candidats du TRKB et la réponse thérapeutique après traitement antidépresseur dans la cohorte METADAP.

Enfin, nous avons étudié les interactions entre ces 8 polymorphismes et les caractéristiques cliniques du TDU sur la réponse après traitement par antidépresseur. Nous n'avons pas trouvé de lien dans la cohorte METADAP.

4.2 LIMITES

Ce travail a certaines limites. Tout d'abord, la cohorte METADAP a un taux d'attrition élevé. Cependant, il semble inhérent à la population étudiée de patients avec un EDC. Ce taux est comparable à des cohortes similaires comme STAR*D [96]. Toutefois, le taux d'attrition n'était pas associé aux polymorphismes génétiques de TRKB, ni aux variables cliniques étudiés, ni à la classe de traitement prescrite, ni à la réponse thérapeutique.

Une autre limite de l'étude est l'absence de groupe placebo. Ainsi l'étude évaluait l'évolution de la dépression en termes de réponse vis-à-vis d'une prise en charge globale médicamenteuse comme non médicamenteuse. Comme de nombreuses études montrent l'efficacité des antidépresseurs dans la dépression [14], cela poserait des problèmes éthiques de proposer un placebo à des patients déprimés sur une période longue (6 mois). Ceci explique que les études similaires n'utilisent pas non plus de placebo.

METADAP est une cohorte naturaliste. La prescription est donc en ouvert et sans randomisation. Les prescripteurs étaient en aveugle de la génétique mais non des caractéristiques cliniques de la dépression. Cela a pu induire un biais de prescription. Pour tenir compte de cet aspect, nous avons ajusté sur les caractéristiques cliniques et sociodémographiques.

Dans la cohorte METADAP, nous n'avons pas les données sur les co-prescriptions et principalement les benzodiazépines qui sembleraient influencer l'évolution de la dépression [196]. Cette cohorte voyait leurs prescriptions limitées à 14 jours à une dose la plus faible possible. Ceci permettait, a priori, d'en diminuer l'impact.

Au niveau des caractéristiques cliniques, certaines d'entre elles, telles que les comorbidités anxieuses ou les troubles de personnalité n'étaient pas disponibles alors qu'elles semblent avoir une influence sur la réponse après traitement par antidépresseur [197].

5 CONCLUSION ET PERSPECTIVES

RAPPEL DES RESULTATS

Les patients déprimés homozygotes CC du rs2289656 du TRKB présentent deux fois plus de tentatives de suicide récentes que les porteurs de l'allèle T. Les autres polymorphismes ne sont pas associés dans notre étude aux caractéristiques cliniques de la dépression. Nous ne trouvons aucune association entre les 8 polymorphismes du TRKB, seuls ou en association avec les caractéristiques cliniques de la dépression, sur la réponse après traitement antidépresseur.

REPLICATION

Ces résultats nécessitent confirmation dans une autre cohorte. Nous pourrions utiliser pour celle-ci les cohortes d'ENIGMA MMD [198] ou de l'UKBIOBANK [199] dont les deux équipes collaborent avec l'équipe INSERM MOODS à laquelle je suis rattaché.

METADAP

Parmi les biomarqueurs génétiques, ceux de la voie de la neurogenèse (TRKB, BDNF et P75NTR) sembleraient avoir un lien avec la réponse après traitement par antidépresseurs [95]. Le BDNF a déjà fait l'objet d'une étude dans MEDATAP [200]. Nous comptons étudier le gène P75NTR dont les données de certains SNP ont déjà été recueillies dans la cohorte MEDATAP.

Cette cohorte a aussi bénéficié d'une technique récente de séquençage, le « next generation sequencing » (NGS), qui permet de détecter un grand nombre de séquences. Nous comptons nous concentrer sur la variabilité du nombre de copies ou « copy number variation » (CNV). Lors de la copie du génome, il peut y avoir des duplications, des délétions, des insertions ou même des inversions. Le CNV d'une séquence de paires de base consiste à regarder la différence du nombre de cette séquence dans les copies du génome. Le nombre de copies de cette variation semble avoir un impact sur le phénotype génétique [201]. Nous proposons d'étudier les données du séquençage par NGS sur les duplications, les délétions, les insertions, les inversions et le CNV de séquences de paires de base du gène TRKB sur la réponse après traitement antidépresseur.

METADAP et DEP-ARREST CLIN

Nous avons montré que les patients déprimés avec une TS récente semblaient avoir des différences biologiques avec les autres patients déprimés. Les patients avec une TS récente ont un plus petit hippocampe [202]. L'imagerie cérébrale pourrait être en lien avec le TRKB.

Nous nous proposons de regarder si les polymorphismes du TRKB combinés aux caractéristiques cliniques sont associés à des différences sur l'imagerie cérébrale.

DEP-ARREST CLIN est une cohorte de 69 patients présentant un EDC, sans traitement antidépresseur depuis au moins 1 mois, nécessitant l'introduction d'un traitement antidépresseur par Venlafaxine et dont la sévérité de l'EDC est évaluée à l'inclusion, à 1 mois et 3 mois de traitement. Ces patients ont aussi bénéficié d'une IRM cérébrale à l'inclusion et à 3 mois, ainsi qu'un génotypage du TRKB. Nous proposons de grouper cette cohorte avec les patients de METADAP, ayant eu une IRM cérébrale à l'inclusion, ce qui nous permettrait d'avoir une cohorte de plus de 120 patients avec une IRM cérébrale.

SCORE COMPOSITE

Nous avons vu que les caractéristiques cliniques semblent avoir une influence sur la réponse après traitement par antidépresseurs dans une population déprimée. Or certains marqueurs biologiques, comme ceux de l'inflammation, sembleraient aussi avoir un impact sur cette réponse [190,203]. La principale perspective de l'étude est de créer, à terme, un score composite, à partir des caractéristiques cliniques, biologiques, génétiques et de l'imagerie, permettant de prédire, dans le TDU, la réponse après traitement par antidépresseurs dans la cohorte MEDATAP et DEP-ARREST CLIN. Plusieurs études sont actuellement menées pour trouver un tel score composite : une étude danoise et une étude canadienne par exemple sont en cours pour élaborer un score composite sur des données similaires associant imagerie, biologie, génétique et caractéristiques cliniques [204,205]. Un score composite de ce type est déjà utilisé dans le cancer du sein. Dans la cohorte MyPEBS, ce score comprenant de la génétique et de la clinique évalue le risque de cancer du sein et sert à ajuster la périodicité de la mammographie [206].

ELARGISSEMENT DU DOMAINE DE RECHERCHE : E3N

Nous avons examiné l'effet des antidépresseurs sur la réponse en fonction de caractéristiques cliniques de la dépression dans une cohorte déprimée sur une période de 6 mois. La suite de ce travail serait d'étudier cet effet en population générale, c'est-à-dire des personnes (déprimées ou pas) que nous voyons en cabinet de médecine générale. La médecine générale gère les pathologies sur le temps long, ce qui est une des limites de la cohorte METADAP.

Nous travaillons en collaboration avec l'équipe « exposome et hérédité » (CESP) sur la cohorte E3N de 100 000 femmes assurées à la MGEN suivies sur plus de 25 ans. Cette équipe a

recueilli des informations sur leurs caractéristiques sociodémographiques, leurs habitudes de vie (sport, tabac, alimentation, etc.), leurs pathologies (y compris des échelles de dépression), leurs traitements et leurs consultations médicales tout au long du suivi. Elle a recueilli aussi des données biologiques et génétiques pour une partie d'entre elles.

Nous avons dans le cadre de ce travail financé par la ligue contre le cancer accès à toutes ces données exceptées pour l'instant les données biologiques et génétiques.

Nous nous proposons d'examiner la prise en charge des personnes déprimées en ambulatoire en matière de suivi en médecine générale et en psychiatrie de ville afin d'étudier l'évolution des femmes déprimées sur plusieurs années en fonction de cette prise en charge globale. Dans le cadre d'une vision plus large de mon domaine de recherche, nous regardons l'effet des antidépresseurs sur d'autres pathologies que la dépression. Notre travail actuel est d'étudier l'effet des antidépresseurs sur la survenue de cancer du sein sur 10 ans.

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7 ANNEXE

Tableau de données supplémentaires

SNP	Position	fonction	A1	A2	Gene	Freq A1	Freq A2
rs1439050	87288192	intron	G	T	NTRK2	0,673	0,327
rs1187352	87293456	intron	A	G	NTRK2	0,358	0,642
rs1778933	87324410	intron	C	T	NTRK2	0,35	0,65
rs2289658	87563369	exon syn	A	G	NTRK2	0,96	0,04
rs2289657	87563459	intron	G	T	NTRK2	0,942	0,058
rs2289656	87563561	intron	C	T	NTRK2	0,832	0,168
rs3824519	87570003	intron	C	T	NTRK2	0,916	0,084
rs56142442	87636264	exon syn	C	T	NTRK2	0,949	0,051

Table S1: studied SNP description

Position: on the chromosome 9 ; A1/2 : Allele 1/2; syn : synonym ; eq : allelic frequency according to the SNPdb.

rs2289656	Acute SA			Lifetime SA		
Genotype	no	yes	p	no	yes	p
Patients (%(n))	77.2 (439)	22.8 (130)		54.3 (309)	45.7 (260)	
Age (m(sd))	47.1* (12.7)	43 (13.8)	0.002	47.1 (13.1)	45.1 (13)	0.07
Women (%(n))	68.3 (300)	73.8 (96)	0.22	66 (204)	73.8 (192)	0.04
Single (%(n))	51 (224)	56.9 (74)	0.23	49.8 (154)	55.4 (144)	0.17
High educational level (%(n))	43.7 (192)	47.7 (62)	0.44	43.7 (135)	45.8 (119)	0.64
Recurrent MDD (%(n))	74.7 (328)	74.6 (97)	0.95	66.3 (205)	84.6 (220)	0.000001
Previous antidepressant treatment (%(n))	80 (351)	73.1 (95)	0.09	76.7 (237)	80.4 (209)	0.32
HAMD (m(sd))	24.2 (4.9)	25.9 (4.9)	0.001	24.2 (4.9)	25.1 (5)	0.02

Table S2 : demographic and clinical features according to acute suicide attempt (SA) and Lifetime SA.

m: mean; sd: standard derivation; n: patients numbers; MDD: Major Depressive Disorder; HAMD- 17: Hamilton depression rating scale 17 item.

SNP	MAH	mAH	MAH	Hz	mAH	Chi2	p
rs1778933	T	C	278	214	54	1.8	0.18
rs1187352	G	A	266	221	59	1.6	0.20
rs2289658	A	G	501	39	4	9.6	0.002
rs2289657	G	T	512	37	2	2.2	0.14
rs2289656	C	T	339	180	26	0.11	0.74
rs3824519	C	T	467	74	9	6.48	0.01
rs56142442	C	T	549	3	0	0.004	0.94
rs1439050	G	T	194	262	73	1.1	0.3

Table S3 : Hardy Weinberg and allelic repartition

MAH: major allelic homozygote, Hz: Heterozygote, mAH: minor allelic homozygote

	rs1439050	rs1187352	rs1778933	rs2289658	rs2289657	rs2289656	rs3824519
rs1439050	1	0.54	0.50	-0.14	-0.12	0.01	-0.14
rs1187352		1	0.75	0.04	0.11	-0.06	0.14
rs1778933			1	0.11	0.13	-0.03	0.10
rs2289658				1	1.00	-1.00	0.79
rs2289657					1	-1.00	0.92
rs2289656						1	-1.00
rs3824519							1
rs56142442							

Table S4: Linkage disequilibrium for the NTRK2 genetic polymorphisms studied.

Linkage disequilibrium matrix present D' criteria value between each SNPs. Moderate linkage disequilibrium was defined by D' criteria absolute value between 0.50 and 0.75. High linkage disequilibrium was defined by D' criteria absolute value between 0.75 and 1.

	rs1439050		rs1187352		rs1778933		rs2289658		rs2289657		rs2289656		rs3824519	
Genotype	G	T	G	A	T	C	A	G	G	T	C	T	C	T
Allelic number	653	411	755	341	775	327	1047	47	1065	41	861	233	1011	93
Age (m(sd))	45,6 ^a (13,2)	47,4 ^a (13,1)	45,9 (13)	46,9 (13,3)	46,2 (13)	46,5 (13,4)	46,2 (13,2)	47,7 (11,4)	46,2 (13,1)	48,5 (11,3)	45,7 ^b (13,3)	48,2 ^b (12)	46,3 (13,2)	45,7 (11,9)
Women (%(n))	70,8 (462)	69,1 (284)	70,5 (532)	69,2 (236)	69,7 (540)	71,6 (234)	71 ^c (743)	57,4 ^e (27)	70,3 (749)	56,1 (23)	69,6 (599)	72,5 (169)	70,1 (709)	65,6 (61)
Single (%(n))	51,5 (336)	54,5 (224)	54 (408)	51,6 (176)	51,2 (397)	56,6 (185)	52,6 (551)	53,2 (25)	52,9 (563)	51,2 (21)	54,5 ^d (469)	46,8 ^d (109)	52,7 (533)	50,5 (47)
High educational level (%(n))	46,2 (302)	40,4 (166)	44,2 (334)	45,7 (156)	44,1 (342)	45,3 (148)	44,6 (467)	44,7 (21)	44,6 (475)	46,3 (19)	46,2 ^e (398)	37,8 ^e (88)	44,2 (447)	41,9 (39)
Smoking (%(n))	38,9 (254)	34,1 (140)	38,3 (289)	33,7 (115)	37 (287)	35,2 (115)	36,4 (381)	36,2 (17)	36,5 (389)	41,5 (17)	35,2 (303)	41,6 (97)	36,4 (368)	43 (40)
Recurrent MDD (%(n))	75,3 (492)	74,5 (306)	74,1 (559)	77,4 (264)	73,5 (570)	78,3 (256)	75,5 (790)	70,2 (33)	75 (799)	75,6 (31)	75,6 (651)	73,3 (171)	74,8 (756)	76,3 (71)
HAMD-17 (m(sd))	24,4 (4,9)	24,7 (4,9)	24,4 (4,9)	24,8 (4,9)	24,5 (4,9)	24,6 (4,8)	24,5 (4,9)	24,8 (5,3)	24,5 (4,9)	24,8 (5,4)	24,5 (5)	24,5 (4,5)	24,5 (4,8)	24,5 (5,4)
Current antidepressant treatment (%(n))	38,4 (251)	35,8 (147)	37,5 (283)	36,1 (123)	37,7 (292)	36,1 (118)	37,1 (388)	38,3 (18)	37,2 (396)	34,1 (14)	38,1 (328)	33,5 (78)	37 (374)	36,6 (34)
Previous antidepressant treatment (%(n))	78,5 (513)	78,6 (323)	77,3 (584)	81,5 (278)	77,2 (598)	81,7 (267)	78,9 (826)	76,6 (36)	78,6 (837)	80,5 (33)	77,7 (669)	81,9 (191)	78,7 (796)	79,6 (74)
Suicide Attempt														
Lifetime SA (%(n))	45 (294)	46,5 (191)	45,7 (345)	46,3 (158)	45,3 (351)	47,7 (156)	45,9 (481)	51,1 (24)	45,7 (487)	53,7 (22)	47,8 (412)	39,2 (91)	45 (455)	53,8 (50)
Past SA (%(n))	31,2 (204)	31,6 (130)	31 (234)	32,8 (112)	30,2 (234)	35,5 (116)	31,9 (334)	34 (16)	31,8 (339)	36,6 (15)	32,5 (280)	29,2 (68)	31,2 (315)	37,6 (35)
Acute SA (%(n))	22,1 (144)	23,4 (96)	22,6 (171)	24,6 (84)	23,2 (180)	23,5 (77)	23,2 (243)	21,3 (10)	23,3 (248)	19,5 (8)	25,7 (221)	14,2 (33)	22,8 (231)	23,7 (22)

Table S5: Demographic and clinical features according to the TRKB alleles.

n: number; *m*: mean; *sd*: standard deviation; HAMD-17: Hamilton Depression Rating Scale 17 items; MDD: Major Depressive Disorder; SA: Suicide Attempt; Past SA: at least one month ago suicide attempt event.

^a: $p=0.02$ (bivariate analysis) for inter-allelic comparisons; ^b: $p=0.01$ (bivariate analysis) for inter-allelic comparisons; ^c: $p=0.05$ (bivariate analysis) for inter-allelic comparisons; ^d: $p=0.04$ (bivariate analysis) for inter-allelic comparisons; ^e: $p=0.02$ (bivariate analysis) for inter-allelic comparisons (3 groups); ^e: age ($p=0.025$ (bivariate analysis) for inter-allelic comparisons).

Level 1A	Annotation for a variant-drug combination in a CPIC or medical society-endorsed PGx guideline, or implemented at a PGRN site or in another major health system.
Level 1B	Annotation for a variant-drug combination where the preponderance of evidence shows an association. The association must be replicated in more than one cohort with significant p-values, and preferably associated with a strong effect size.
Level 2A	Annotation for a variant-drug combination that qualifies for level 2B where the variant is within a VIP (Very Important Pharmacogene) as defined by PharmGKB. The variants in level 2A are in known pharmacogenes, so functional significance is more likely.
Level 2B	Annotation for a variant-drug combination with moderate evidence of an association. The association must be replicated but there may be some studies that do not show statistical significance, and/or the effect size may be small.
Level 3	Annotation for a variant-drug combination based on a single significant (not yet replicated) or annotation for a variant-drug combination evaluated in multiple studies but lacking clear evidence of an association.
Level 4	Annotation based on a case report, non-significant study or in vitro, molecular or functional assay evidence only.

Table S6: clinical annotation level of evidence (PharmGKB)

Study	SNP	Location	Biological Effect	Minor Allele	MAF	n	Ethnicity	Diagnosis	AD	Genotype with higher efficacy	Significant Outcome	L.E.	Ref
Gratacos et al., 2008	rs10501087	3' UTR	Unknown	C	0.26	374	Caucasian	MDE	F/P/S/C/V	no	no	3	[124]
Kocabas et al., 2011				na	na	206	Caucasian	MDE-MDD	all marketed AD	C	Response : OR=2.06 95%CI (1.23–3.45), p=0.009	3	[136]
Gratacos et al., 2008	rs1491850	5'UTR	Unknown	C	0.43	374	Caucasian	MDE	F/P/S/C/V	no	no	3	[124]
Kocabas et al., 2011				na	na	206	Caucasian	MDE-MDD	all marketed AD	C	Response : OR=1.88 95%CI (1.23–2.88), p=0.007	3	[136]
Hennings et al., 2013	rs2049046	intron	Unknown	C	na	894	Caucasian	MDE	all marketed AD	no	no	3	[41]
Hennings et al., 2013				A	na	894	Caucasian	MDE	all marketed AD	T	Response : p=0.02	3	[41]
Licinio et al., 2009	rs61888800	intron	Unknown	na	na	272	Mexican American	MDE-MDD	F/D	GG	Response : p=0.02	3	[128]
Illi et al., 2013				T	0.25	106	Caucasian	MDE-MDD	C/F/P	no	no	3	[143]
Tsai et al., 2003	rs6265	exon missense	Met= Decrease dendritic trafficking	Met	0.54	152	Asian	MDE-MDD	F	no	no	3	[121]
Choi et al., 2006				Met	0.54	128	Asian	MDE-MDD	C	Met	Score : p=0.03 Response : OR=4.375, 95%CI (1.61–11.9), p=0.003	3	[122]
Wilkie et al., 2007				Met	0.16	166	Caucasian	MDE-MDD	P/C/I/L/Ph	no	no	3	[123]
Gratacos et al., 2008				Met	0.23	374	Caucasian	MDE	F/P/S/C/V	no	no	3	[124]
Lin et al., 2008				Met	0.51	72	Asian	MDE-MDD	V	no	no	3	[125]
Yoshida et al., 2008				Met	0.41	134	Asian	MDE-MDD	Fv/Ml	Met	Score : p=0.0004	3	[126]
Licinio et al., 2009]				Met	0.10	272	Mexican American	MDE-MDD	F/D	no	no	3	[128]
Alexopoulos et al., 2010				Met	0.28	34	Caucasian	geriatric MDE-MDD	E	Met	Remission : p=0.04	3	[129]
Bukh et al., 2010				Met	na	290	Caucasian	MDE-MDD	all marketed AD	no	no	3	[130]
Domschke et al., 2010				Met	0.20	268	Caucasian	MDE-MDD	all marketed AD	no	no	3	[131]
Kang et al., 2010				Met	0.52	243	Asian	MDE-MDD	M	no	no	3	[132]
Lañcot et al., 2010				Met	0.19	90	Caucasian	MDE-MDD	C	Val/Val	Score : 0.02	3	[133]
Pae et al., 2010]				Met	0.48	141	Asian	MDE-MDD	all marketed AD	no	no	3	[134]
Taylor et al., 2011				Met	na	229	Caucasian	geriatric MDE-MDD	all marketed AD	Met	Remission: p=0.049	3	[138]
Zou et al., 2010]				Met	0.48	305	Asian	MDE-MDD	F	no	no	3	[135]
Kocabas et al., 2011				na	na	206	Caucasian	MDE-MDD	all marketed AD	Met	Response : OR=2.07, 95%CI (1.22–3.51), p=0.01	3	[136]
Su et al., 2011				Met	0.53	166	Asian	Alcohol+MD E-MDD	S	Met	Response : OR=2.17, 95%CI (1.39-3.42), p=0.001	3	[137]
Yoshimura et al., 2011				Met	0.35	132	Asian	MDE-MDD	P/S	no	no	3	[139]
Katsuki et al., 2012]				na	na	84	Asian	MDE-MDD	M	no	no	3	[140]
Musil et al., 2012				Met	0.19	324	Caucasian	MDE	all marketed AD	no	no	3	[141]
Xu et al., 2012				Met	na	159	Asian	MDE-MDD	SSRI 104/V 55	Met	SSRI: Score: p=0.02 SSRI: Response: OR=4.85, 95%CI (1.04-22.58), p=0.04	3	[142]
Hennings et al., 2013				Met	na	894	Caucasian	MDE	all marketed AD	no	no	3	[41]
Li et al., 2013				Met	0.48	948	Asian	MDE-MDD	all marketed AD	no	no	3	[42]
El Hage et al., 2014				Met	0.25	187	Caucasian	MDE	E	Met	Response : p=0.02	3	[144]
Liu et al., 2014				na	na	155	Asian	MDE with CD	S	Met	Response : OR=2.14, 95%CI (1.29-3.53), p=0.003	3	[145]
Matsumoto et al., 2014				Met	0.24	97	Caucasian	MDE	all marketed AD	no	no	3	[146]
Colle et al., 2015	Met	0.19	345	Caucasian	MDE-MDD	SSRI/SNRI/TCA	Met Val/Val	SSRI: Response: OR: 3.04, 95%CI (1.05-9.37), p=0.04 SNRI/TCA: Remission: OR=0.27, 95%CI (0.09; 0.76), p=0.02	3	[147]			

First Author (continuous)	SNP	Location	Function	Biological Effect	Minor Allele	MAF	n	Ethnicity	Treatment	Diff in Efficacy	L.E.	Ref
Dong et al., 2009	NT_023935.17_16450226	exon	nonsense	?	T	0.00	142	mexican american	F/D	no	4	[40]
	NT_023935.17_16481780	intron		?	C	0.00						
	NT_023935.17_16490299	intron		?	T	0.00						
	NT_023935.17_16502988	intron		?	G	0.00						
	NT_023935.17_16503239	intron		?	G	0.00						
	NT_023935.17_16503845	intron		?	A	0.00						
	NT_023935.17_16507180	exon	synonymous	?	A	0.00						
	NT_023935.17_16507266	exon	nonsense	?	T	0.00						
	NT_023935.17_16521302	intron		?	A	0.00						
	NT_023935.17_16521313	intron		?	C	0.00						
	NT_023935.17_16590123	3' UTR		?	C	0.00						
	NT_023935.17_16590662	3' UTR		?	G	0.01						
	NT_023935.17_16590716	3' UTR		?	C	0.00						
	NT_023935.17_16590955	3' UTR		?	G	0.00						
	NT_023935.17_16590990	3' UTR		?	T	0.00						
	NT_023935.17_16591153	3' UTR		?	T	0.00						
	NT_023935.17_16591468	3' UTR		?	A	0.01						
	NT_023935.17_16591473	3' UTR		?	C	0.00						
	NT_023935.17_16592191	3' UTR		?	G	0.00						
	NT_023935.17_16592497	3' UTR		?	G	0.00						
	NT_023935.17_16592666	3' UTR		?	T	0.00						
	NT_023935.17_16592772	3' UTR		?	C	0.00						
	NT_023935.17_16592920	3' UTR		?	C	0.00						
	NT_023935.17_16593023	3' UTR		?	T	0.00						
	NT_023935.17_16593178	3' UTR		?	A	0.00						
	NT_023935.17_16593339	3' UTR		?	T	0.13						
	NT_023935.17_16593340	3' UTR		?	G	0.13						
	NT_023935.17_16593603	3' UTR		?	G	0.00						
	NT_023935.17_16594152	3' UTR		?	G	0.00						
	NT_023935.17_16594857	3' UTR		?	T	0.00						
NT_023935.17_16594911	3' UTR		?	C	0.00							

First Author (continuous)	SNP	Location	Function	Biological Effect	Minor Allele	MAF	n	Ethnicity	Treatment	Diff in Efficacy	L.E.	Ref
Dong et al., 2009	NT_023935.17_16594963	3' UTR		?	G	0.00	142	mexican american	F/D	no	4	[40]
	NT_023935.17_16646582	intron		?	G	0.00						
	NT_023935.17_16651920	3' UTR		?	C	0.06						
	NT_023935.17_16653522	3' UTR		?	T	0.00						
	NT_023935.17_16653882	3' UTR		?	A	0.00						
	NT_023935.17_16653919	3' UTR		?	A	0.00						
	NT_023935.17_16654443	3' UTR		?	A	0.00						
	NT_023935.17_16655632	3' UTR		?	G	0.00						
	NT_023935.17_16655995	3' UTR		?	G	0.00						
	NT_023935.17_16656574	3' UTR		?	G	0.00						
	NT_023935.17_16656579	3' UTR		?	T	0.00						
	NT_023935.17_16656587	3' UTR		?	G	0.00						
	NT_023935.17_16656677	3' UTR		?	A	0.00						
	NT_023935.17_16656782	3' UTR		?	A	0.05						
	NT_023935.17_16656796	3' UTR		?	T	0.05						
	NT_023935.17_16657062	3' UTR		?	A	0.01						
	NT_023935.17_16657071	3' UTR		?	A	0.00						
	NT_023935.17_16657106	3' UTR		?	G	0.01						
	NT_023935.17_16657232	3' UTR		?	G	0.00						
	NT_023935.17_16657257	3' UTR		?	A	0.00						
	NT_023935.17_16657345	3' UTR		?	T	0.07						
	NT_023935.17_16657393	intron		?	T	0.02						
NT_023935.17_16799618	intron		?	A	0.00							
NT_023935.17_16800728	Exon	synonymous	?	A	0.01							
NT_023935.17_16800996	3' UTR		?	G	0.01							
NT_023935.17_16801558	3' UTR		?	A	0.00							
Hennings et al., 2013	rs1047896	intron		?	A	0.19	894	caucasian	all marketed AD	no	4	[41]
	rs10512159	intron		?	A	0.16						
Dong et al., 2009	rs10780691	3' UTR		?	T	0.47	142	mexican american	F/D	no	4	[40],
Hennings et al., 2013	rs1078947	intron		?	G	0.15	894	caucasian	all marketed AD	no	4	[41]
	rs10868235	intron		?	T	0.46						

First Author (continuous)	SNP	Location	Function	Biological Effect	Minor Allele	MAF	n	Ethnicity	Treatment	Diff in Efficacy	L.E.	Ref
Hennings et al., 2013	rs10868241	intron		?	C	0.28	894	caucasian	all marketed AD	no	4	[41]
	rs11140714	5' UTR*		?	G	0.24						
	rs11140771	intron		?	T	0.20						
	rs11140776	intron		?	T	0.46						
	rs11140783	intron		?	T	0.09						
Dong et al., 2009	rs11140793	intron		?	C	0.16	142	mexican american	F/D	no	4	[40]
Hennings et al., 2013	rs11140793	intron		?	C	0.15	894	caucasian	all marketed AD	no	4	[41]
	rs11140800	intron		?	C	0.41						
	rs11140803	intron		?	A	0.17						
	rs11140810	intron		?	T	0.44						
Dong et al., 2009	rs11416761	3' UTR		?	T	0.00	142	mexican american	F/D	no	4	[40]
Hennings et al., 2013	rs1147198	5' UTR*		?	C	0.22	894	caucasian	all marketed AD	no	4	[41]
	rs1187274	intron		?	G	0.30						
	rs1187286	intron		?	G	0.24						
Dong et al., 2009	rs1187326	intron		?	C	0.23	142	mexican american	F/D	no	4	[40]
Hennings et al., 2013	rs1187329	intron		?	A	0.45	894	caucasian	all marketed AD	no	4	[41]
	rs1187363	intron		?	A	0.19						
Dong et al., 2009	rs1221	3' UTR		?	T	0.17	142	mexican american	F/D	no	4	[40]
Hennings et al., 2013	rs12338909	intron		?	C	0.10	894	caucasian	all marketed AD	no	4	[41]
Li et al., 2013	rs1387923	3' UTR		?	C	0.25	948	Asian	all marketed AD	no	4	[42]
Hennings et al., 2013	rs1387924	intron		?	A	0.17	894	caucasian	all marketed AD	no	4	[41]
	rs1387926	intron		?	T	0.12						
	rs1439050	intron		?	T	0.35						
	rs1443440	intron		?	G	0.29						
	rs1443445	intron		?	T	0.20						
	rs1490402	3' UTR*		?	T	0.14						
	rs1490403	3' UTR		?	C	0.28						
	rs1619120	intron*		?	T	0.42						
Dong et al., 2009	rs1624327	intron		?	A	0.25	142	mexican american	F/D	no	4	[40]
Hennings et al., 2013	rs1627784	intron		?	G	0.27	894	caucasian	all marketed AD	no	4	[41]
	rs1662695	intron		?	C	0.13						

First Author (continuous)	SNP	Location	Function	Biological Effect	Minor Allele	MAF	n	Ethnicity	Treatment	Diff in Efficacy	L.E.	Ref
Hennings et al., 2013	rs17418241	intron		?	T	0.09	894	caucasian	all marketed AD	no	4	[41]
Dong et al., 2009	rs1778929	intron		?	T	0.36	142	mexican american	F/D	no	4	[40]
Hennings et al., 2013	rs1778931	intron		?	A	0.49	894	caucasian	all marketed AD	no	4	[41]
	rs1778933	intron		?	C	0.36						
	rs1822420	intron		?	T	0.14						
	rs1867283	intron		?	A	0.49						
	rs1948308	intron		?	T	0.44						
Dong et al., 2009	rs2013566	intron		?	G	0.15	142	mexican american	F/D	no	4	[40]
Hennings et al., 2013	rs2165893	intron		?	G	0.06	894	caucasian	all marketed AD	no	4	[41]
	rs2277192	intron		?	G	0.15						
	rs2277193	intron		?	C	0.28						
Dong et al., 2009	rs2289656	intron		?	A	0.09	142	mexican american	F/D	no	4	[40]
Hennings et al., 2013	rs2289656	intron		?	A	0.17	894	caucasian	all marketed AD	no	4	[41]
Dong et al., 2009	rs2289657	intron		?	A	0.10	142	mexican american	F/D	no	4	[40]
	rs2289658	exon	synonymous	?	C	0.16						
Hennings et al., 2013	rs2378672	intron*		?	G	0.08	894	caucasian	all marketed AD	no	4	[41]
	rs2586566	intron*		?	G	0.23						
Li et al., 2013	rs2769605	nc	nc	?	A	0.22	948	Asian	all marketed AD	no	4	[42]
Hennings et al., 2013	rs2808707	intron		?	T	0.40	894	caucasian	all marketed AD	no	4	[41]
	rs3739570	3' UTR		?	C	0.10						
	rs3739804	intron		?	G	0.08						
Dong et al., 2009	rs3739806	3' UTR		?	C	0.07	142	mexican american	F/D	no	4	[40]
	rs3739807	intron		?	T	0.13						
Hennings et al., 2013	rs3758317	5' UTR near gene		?	T	0.20	894	caucasian	all marketed AD	no	4	[41]
	rs3824519	intron		?	G	0.08						
	rs3860945	intron		?	T	0.14						
Dong et al., 2009	rs41277883	3' UTR		?	G	0.01	142	mexican american	F/D	no	4	[40]
	rs41277885	3' UTR		?	G	0.00						
	rs41277889	3' UTR		?	A	0.00						
	rs41282429	3' UTR		?	T	0.00						
	rs41282435	3' UTR		?	G	0.02						

First Author (continuous)	SNP	Location	Function	Biological Effect	Minor Allele	MAF	n	Ethnicity	Treatment	Diff in Efficacy	L.E.	Ref
Dong et al., 2009	rs41282437	3' UTR		?	T	0.01	142	mexican american	F/D	no	4	[40]
	rs41318035	intron		?	A	0.02						
Hennings et al., 2013	rs4361832	intron		?	C	0.18	894	caucasian	all marketed AD	no	4	[41]
	rs4486281	intron		?	G	0.29						
Dong et al., 2009	rs45596934	intron		?	A	0.13	142	mexican american	F/D	no	4	[40]
	rs56142442	exon	synonimus	?	T	0.05						
	rs56407004	3' UTR		?	C	0.00						
	rs58830583	3' UTR		?	A	0.01						
Hennings et al., 2013	rs614886	3' UTR		?	G	0.30	894	caucasian	all marketed AD	no	4	[41]
Dong et al., 2009	rs6559833	3' UTR		?	C	0.35	142	mexican american	F/D	no	4	[40]
Hennings et al., 2013	rs6559836	intron		?	A	0.17						
	rs6559840	intron		?	G	0.27						
	rs681329	3' UTR*		?	T	0.12						
Dong et al., 2009	rs7020204	intron		?	T	0.12	142	mexican american	F/D	no	4	[40]
Hennings et al., 2013	rs7023589	intron		?	T	0.35	894	caucasian	all marketed AD	no	4	[41]
	rs7026417	intron		?	C	0.10						
Dong et al., 2009	rs7038236	intron		?	A	0.15	142	mexican american	F/D	no	4	[40]
	rs7047042	3' UTR		?	G	0.16						
Hennings et al., 2013	rs7048015	intron		?	C	0.18	894	caucasian	all marketed AD	no	4	
Dong et al., 2009	rs730240	3' UTR		?	T	0.00	142	mexican american	F/D	no	4	[40]
Hennings et al., 2013	rs7855888	intron		?	C	0.25	894	caucasian	all marketed AD	no	4	[41]
	rs7859023	intron		?	G	0.15						
	rs7875184	intron		?	T	0.14						
	rs984430	intron		?	A	0.17						
Dong et al., 2009	rs9969761	3' UTR		?	G	0.09	142	mexican american	F/D	no	4	[40]
	rs9969765	intron		?	C	0.40						
Hennings et al., 2013	rs9969765	intron		?	G	0.33	894	caucasian	all marketed AD	no	4	[41]

Table S7 BDNF Polymorphisms with no reported association with antidepressant efficacy

AD: Antidepressant; C: Citalopram; CD: Coronary disease; D: Desipramine; E: Escitalopram; F: Fluoxetine; Fv: Fluvoxamine; I: Imipramine; L: Lofepamine; L.E.: Level of evidence; M: Mirtazapine; MAF: Minor allele frequency; MDD: Major depressive disorder; MDE: Major depressive episode; Mi: Minalcipran; NA: Not available; OR: Odds ratio; P: Paroxetine; Ph: Phenelezine; S: Sertraline; SNRI: Serotonin and norepinephrine reuptake inhibitor; SSRI: Serotonin selective reuptake inhibitor; Ref: Reference, TCA: Tricyclic antidepressant; V: Venlafaxine.

Study (continuous)	SNP	Location	Biological Effect	Minor Allèle	MAF	n	Ethnicity	Diagnosis	AD	Genotype with higher efficacy	Significant Outcome	L.E.	Ref	
Domschke et al., 2010	rs7103411	Intron	Unknown	C	0.22	268	Caucasian	MDE-MDD	all marketed AD	C	Score: Male: p=.009, Anxious: p=0.005 Melancolic: p=0.003	3	[131]	
Musil et al., 2012				C	0.22	324	Caucasian	MDE-MDD	all marketed AD	no		no	3	[141]
Licinio et al., 2009	rs7124442	Exon	Unknown	C	0.23	272	Mexican American	MDE-MDD	F/D	no	no	3	[128]	
Domschke et al., 2010				C	0.31	268	Caucasian	MDE-MDD	all marketed AD	CC	Score : p=0.01	3	[131]	
Musil et al., 2012				C	0.28	324	Caucasian	MDE	all marketed AD	no	no	3	[141]	
Gratacos et al., 2008	rs908867	5' UTR	Unknown	A	0.07	374	Caucasian	MDE	F/P/S/C/V	A	Remission : OR=3.57, 95%CI (1.51-8.16), p=0.003	3	[124]	
Kocabas et al., 2011				na	na	206	Caucasian	MDD-MDD	all marketed AD	no		no	3	[136]
Licinio et al., 2009				A	0.04	272	Mexican American	MDE-MDD	F/D	no		no	3	[128]

Table S8 TRKB Polymorphisms with no reported association with antidepressant efficacy

AD: Antidepressant; D: Desipramine; F: Fluoxetine; L.E.: Level of evidence; MAF: Minor allele frequency; Ref: Reference

Titre : Polymorphismes génétiques du TRKB, caractéristiques cliniques et réponse après traitement antidépresseur dans le trouble dépressif unipolaire

Mots clés : réponse après traitement antidépresseur, polymorphisme génétique, pharmacogénétique, TRKB, caractéristique clinique, épisode dépressif caractérisé

Abstract : Introduction Les études sur l'Animal et l'Homme montrent que le Récepteur Tyrosine-Kinase B (TRKB), principal récepteur du Brain Derived Neurotrophic Factor (BDNF), est impliqué dans le trouble dépressif unipolaire (TDU) et le mécanisme d'action des antidépresseurs. Les variations génétiques du TRKB pourraient être un biomarqueur des caractéristiques cliniques de l'épisode dépressif caractérisé (EDC) et prédire la réponse après traitement antidépresseur. Notre objectif est d'examiner l'association entre des polymorphismes génétiques du TRKB et les caractéristiques cliniques de la dépression et la réponse après traitement antidépresseur chez des patients déprimés. **Méthodes** Les données originales de ce travail sont issues de la cohorte METADAP. Il s'agit d'une cohorte prospective ouverte et naturaliste, multicentrique incluant 624 patients présentant un EDC dans le cadre d'un trouble dépressif caractérisé unipolaire et nécessitant l'introduction d'un traitement antidépresseur. Nous avons évalué 8 polymorphismes nucléotidiques simples (SNP) du TRKB, rs1778933, rs1187352, rs2289658, rs2289657, rs2289656, rs3824519, rs56142442 et rs1439050 ainsi que les caractéristiques cliniques :

les antécédents de tentative de suicide (TS) (ancienne (>1 mois) ou récente (<1 mois)), les antécédents d'EDC et de traitement par antidépresseur et la sévérité de l'EDC actuel. La réponse après traitement antidépresseur était évaluée après 1, 3 et 6 mois de traitement. **Résultats** 1) Le génotype CC du rs2289656 est associé à une augmentation des TS récentes. 2) La revue de la littérature met en évidence une association entre rs10868223, rs11140778, rs1565445 et rs1659412, et réponse après traitement antidépresseur. 3) Nos données ne mettent pas en évidence d'association significative entre les 8 SNP du TRKB et la réponse après traitement antidépresseur. 4) Nous n'avons pas mis en évidence d'interactions entre SNP et caractéristiques cliniques sur la réponse après traitement. **Conclusion** Les patients homozygotes CC pour le rs2289656 présentent deux fois plus de tentatives de suicide récentes que les porteurs de l'allèle T. Aucune autre association n'est observée entre les 8 SNPs du TRKB et les caractéristiques cliniques de l'EDC d'une part et la réponse après traitement antidépresseur d'autre part.

Title : TRKB genetic polymorphisms, clinic features and antidepressant response in the unipolar depressive disorder

Keywords : antidepressant response, genetic polymorphism, pharmacogenetics, trkb, clinical features, major depressive episode

Abstract : Introduction Animal and human studies show that the Tyrosine Kinase B Receptor (TRKB), the main receptor for Brain Derived Neurotrophic Factor (BDNF), is involved in major depressive disorder (MDD) and the antidepressant mechanism of action. Genetic variations in TRKB could be a biomarker of the clinical features of the major depressive episode (MDE) and predict the response after antidepressant treatment. Our objective is to examine the association between TRKB genetic polymorphisms and clinical features of depression and response after antidepressant treatment in depressed patients. **Methods** The original data for this work are from the METADAP cohort. This is a prospective, open, naturalistic, multicenter, prospective cohort including 624 patients with MDE in a mood depressive disorder requiring the introduction of naturalistically prescribed antidepressant therapy. We evaluated 8 single nucleotide polymorphisms (SNPs) of TRKB, rs1778933, rs1187352, rs2289658, rs2289657, rs2289656, rs3824519, rs56142442 and

rs1439050 as well as their clinical characteristics : history of (past (>1 month) or acute (<1 month)) suicide attempt (SA), history of MDE and antidepressant treatment and severity of current MDE. Response after antidepressant treatment was assessed after 1, 3 and 6 months of treatment. **Results** 1) The CC genotype of rs2289656 is associated with an increase of acute SA. 2) The literature review showed an association between rs10868223, rs11140778, rs1565445 and rs1659412 and response after antidepressant treatment. 3) Our data do not show a significant association between the 8 SNPs of TRKB and response after antidepressant treatment. 4) We did not demonstrate any interactions between SNPs and clinical features on post-treatment response. **Conclusion** Homozygous CC patients for rs2289656 had twice as many recent suicide attempts as T-allele carriers. No other association is observed between the 8 SNPs of TRKB and clinical features of MDE on the one hand and antidepressant response on the other hand.