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ORIGINAL RESEARCH

The functional variant rs334558 of *GSK3B* is associated with remission in patients with depressive disorders

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Purpose: *GSK3B* and *AKT1* genes have been implicated in the pathogenesis of a number of psychiatric and neurological disorders. Furthermore, their genetic variants are associated with response to antidepressant pharmacotherapy. As the evidence is still incomplete and inconsistent, continuing efforts to investigate the role of these two genes in the pathogenesis and treatment of brain disorders is necessary. The aim of our study was thus to evaluate the association of variants of these two genes with depressive disorders and drug treatment response.

Patients and methods: In the present study, 222 patients with a depressive disorder who underwent pharmacological antidepressant treatment were divided into remitters and non-remitters following a 28-day course of pharmacotherapy. The association of a depressive disorder and remission rates with polymorphisms rs334558 in the *GSK3B* gene and rs1130214 and rs3730358 in the *AKT1* gene was evaluated with a chi-square test.

Results: Neither of the studied genetic variants was associated with a depressive disorder. Furthermore, frequencies of alleles and genotypes for rs1130214 and rs3730358 were not different in the groups of remitters and non-remitters. However, the activating allele T of the functional polymorphism rs334558 was significantly associated with remission, when all types of antidepressant drugs were included. This association continued as a trend when only patients taking selective serotonin reuptake inhibitors were considered.

Conclusion: The present study provides support that the functional polymorphism rs334558 of *GSK3B* may play a role as a useful genetic and pharmacogenetic biomarker in the framework of personalized medicine approach.

Keywords: depressive disorder, association study, *AKT1*, *GSK3B*, genetic biomarker

Introduction

Depressive disorders are the third leading cause of disability worldwide, according to a 2015 report.[1] The phenotype is complex, indicating the existence of numerous types and subtypes,[2] as are genetic factors contributing to these disorders.[3–5] Inheritance of one type, major depressive disorder (MDD), is only 30–40%, as was shown by twin studies.[6,7] Therefore, environmental factors, translated as epigenetics, must play a substantial role in the etiology.[8,9] Despite the apparent difficulties in the study of genetics of depressive disorders, there have been some breakthroughs in the last several years.[4] An apparent reason that replicable results in genetic studies of depressive disorders have been difficult to achieve is that the patients constitute a very heterogeneous group and the most appropriate approach would be to view depressive disorders from the angle of personalized medicine.[10–19] An example of personalized approach is Research

Domain Criteria that take account of molecular factors in the pathogenesis of mental illnesses.[20–22] This approach is particularly relevant, given the fact that, for example, MDD is pharmacotherapy-resistant in 30–40% of cases.[23] Indeed, without understanding the precise etiopathological mechanisms in different groups of patients, it will not be possible to treat these disorders efficiently.

An important volume of pharmacogenetic studies of depressive disorders exists, including genome-wide association studies and case–control association studies using candidate genes[24–28] (pharmacoepigenetics of depressive disorders is also a developing field[29]). One of the candidate genes used in pharmacogenetic studies in psychiatry is *AKT1*, a gene implicated in the pathogenesis of psychiatric disorders and response to medication via the AKT/GSK3 pathway.[28,30–34] Single nucleotide polymorphisms (SNPs) rs1130214 and rs3730358 in this gene were investigated in the present study because of association of the TC haplotype with lower protein levels of AKT1, which suggests impaired mRNA expression or processing.[34] In addition, SNP rs3730358 was found to be associated with late-onset depression.[35] Another candidate gene is *GSK3B*, one of the major regulators of multiple molecular pathways, including WNT[36,37] and AKT/GSK3 pathways.[30,32] In fact, implication of GSK3B and of its pathways in psychiatric disorders has been extensively investigated.[32–34,38–48] This gene is directly or indirectly inhibited by antipsychotics, lithium, and antidepressants.[30,31] The variant rs334558, found in the promoter of *GSK3B*, is known to be functional, as it determines the expression level of *GSK3B*, possibly by regulating the transcription factor binding to the promoter.[49] In particular, the allele T is associated with a 1.4-fold increased transcriptional strength, compared to the ancestral allele C, apparently because the nucleotide T creates a new binding site at the promoter for the transcription factor AP4.

In the present study, we report the association of remission following pharmacological antidepressant treatment with the functional SNP rs334558. Other SNPs and phenotypes showed no association.

Patients and methods

Study subjects

The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki 1975, revised in Fortaleza, Brazil, 2013) for experiments involving humans. After approval of the study protocol by the Local Bioethics Committee of the Mental Health Research Institute in Tomsk, Russia (Siberian region), 222 patients were recruited from an inpatient facility of the same institute. One hundred and twenty-seven control subjects without psychiatric disorders were also recruited into the study. Only subjects of European ancestry were considered. All subjects gave written informed consent after a proper explanation of the prospective study.

In particular, we included patients with a depressive disorder, determined using the following diagnostic criteria of the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10): depressive episode (ICD-10: F32, 44.4%), recurrent depressive disorder (ICD-10: F33, 34.4%), bipolar disorder (ICD-10: F31, 15.3%), and dysthymia (ICD-10: F34.1, 2.9%). The available demographic data comprised age (18–70 years or 49.93 ± 10.76 years), gender (177 women and 45 men), education (university 43.8%, professional college 44.4%, secondary school 11.8%), employment (employed 68.4%, unemployed or retired 31.6%), and marital status (married 53.2%, widowed 19.3%, divorced 17%, single 10.5%).

Clinical and demographic data were initially recorded in hard-copy medical files by psychiatrists at the Department of Affective Disorders of the Mental Health Research Institute in Tomsk, and this work was supervised by Dr. German Simutkin. These collected data were then transferred to a digital file (an electronic database) and were extracted from it during our study.

During their follow-up in the clinic, patients were given several different groups of antidepressants: selective serotonin reuptake inhibitors (SSRIs) (escitalopram, fluoxetine, paroxetine, fluvoxamine, sertraline, citalopram) (57.9% of patients), tricyclic antidepressants (clomipramine, pipofezine) (20.0%), serotonin–norepinephrine reuptake inhibitors (duloxetine, venlafaxine) (7.1%), noradrenergic and specific serotonergic antidepressants (mirtazapine, mianserin) (2.7%), and agomelatine (12.3%). All antidepressants were used in recommended average therapeutic doses. The duration of treatment was not less than 28 days. For definition of remission, Hamilton Depression Rating scale 17 items (HDRS-17)[50] was used. The evaluation was made on the 28th day of treatment. Remitters were identified if the HDRS-17 scores were ≤7.

Genotyping

Evacuated blood collection tubes "Vacutainer" (Becton Dickinson, Franklin Lakes, NJ, USA) with EDTA as the anticoagulant were used. Extraction of DNA from whole venous blood was performed using the phenol–chloroform method. Concentration and purity of DNA were measured

using NanoDrop 8000 UV-Vis (ultraviolet-visible) spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA).

SNPs rs334558 of the *GSK3B* gene and rs1130214 and rs3730358 of the *AKT1* gene were genotyped by polymerase chain reaction (PCR) using the fluorogenic 5′-exonuclease TaqMan technology and the real-time PCR system "StepOnePlus" (Applied Biosystems, Foster City, CA, USA).

Statistical procedures

Statistical analyses were performed using SPSS software, V 20.0 (IBM Corporation, Armonk, NY, USA) for Windows. Pearson's chi-square test was used for the between-group comparison of genotypic and allelic frequencies at significance level $\alpha = 0.05$. Deviation from Hardy–Weinberg equilibrium of genotypic frequencies was also calculated with a chi-square test.

Results

Of the three SNPs tested, none were associated with depressive disorders when genotypes and alleles were compared between cases and controls. Association was significant only for the SNP rs334558, constituted by alleles T and C, when the group of remitters was compared to non-remitters, for all pharmacological classes of medication taken together. Allele T was found to be associated with remission after 28 days of treatment. In particular, genotypes and alleles were different between remitters and non-remitters, at $p = 0.049$ and $p = 0.015$, respectively (odds ratio [OR] genotype T/T = 2.49, 95% CI: 0.98–6.30; OR allele T = 2.19, 95% confidence interval [CI]: 1.01–4.75). There was no deviation from Hardy–Weinberg equilibrium in the groups of remitters and non-remitters. Table 1 shows these results.

We also measured the association separately for the SSRI group, a class of medication used by the greatest proportion of patients in the cohort. Results of comparison between remitters and non-remitters, shown in Table 2, were significant, at $p = 0.039$, only when alleles were compared, but not genotypes (OR genotype T/T = 3.05, 95% CI: 0.83–11.22; OR allele T = 2.37, 95% CI: 0.82–6.86). The same as for all classes of medication taken together, in the SSRI group remission was associated with allele T.

Discussion

Previous studies presented apparently conflicting results for rs334558, some reporting association of neurological and psychiatric phenotypes, such as Parkinson's disease, Alzheimer's disease, bipolar disorder, schizophrenia, adverse reaction to medication tardive dyskinesia, and resistance to treatment in the case of MDD and bipolar disorder, with the activating allele T,[49,51–59] while others identified allele C as potentially pathogenic in the case of Alzheimer's disease and multiple sclerosis.[60,61] Meta-analyses similarly reported either allele T associated with Alzheimer's disease and MDD,[62,63] or allele C associated with schizophrenia.[64]

Table 1 Distribution of alleles and genotypes of *GSK3B* and *AKT1* polymorphisms in groups of remitters and non-remitters

Polymorphism, allele frequencies (%)*	Genotype, allele	Remitters (%)	Non-remitters (%)	Hardy–Weinberg equilibrium (χ^2, p)	χ^2, p
GSK3B					
	T/T	31.1	15.8	$\chi^2_1 = 0.082$, $p_1 = 0.775$; $\chi^2_2 = 0.139$, $p_2 = 0.709$	$\chi^2 = 6.022$, $p = 0.049$
rs334558	C/T	50.3	50.0		
T = 71.2	C/C	18.6	34.2		
C = 28.8	T	56.3	40.8		$\chi^2 = 5.919$, $p = 0.015$
	C	43.7	59.2		
AKT1					
	G/G	47.3	55.0	$\chi^2_1 = 1.384$, $p_1 = 0.239$; $\chi^2_2 = 3.265$, $p_2 = 0.071$	$\chi^2 = 1.366$, $p = 0.505$
rs1130214	G/T	40.0	30.0		
G = 72.2	T/T	12.7	15.0		
T = 27.8	G	67.3	70.0		$\chi^2 = 0.219$, $p = 0.640$
	T	32.7	30.0		
	C/C	72.7	65.0	$\chi^2_1 = 0.539$, $p_1 = 0.463$; $\chi^2_2 = 0.178$, $p_2 = 0.673$	$\chi^2 = 1.150$, $p = 0.563$
rs3730358	C/T	24.2	32.5		
C = 80.8	T/T	3.0	2.5		
T = 19.2	C	84.8	81.2		$\chi^2 = 0.625$, $p = 0.429$
	T	15.2	18.8		

Notes: Numbers 1 and 2 in subscript represent group of remitters and group of non-remitters, respectively. *The allele frequencies are in the reference population of 198 Utah (USA) residents with Northern and Western European ancestry, as listed in the 1000 Genomes Project, Phase 3 (population CEU).

Table 2 Distribution of alleles and genotypes of rs334558 in groups of remitters and non-remitters (selective serotonin inhibitors only)

Polymorphism	Genotype, allele	Remitters (%)	Non-remitters (%)	Hardy–Weinberg equilibrium (χ^2, p)	χ^2, p
rs334558	T/T	33.7	14.3	$\chi^2_1 = 0.001$, $p_1 = 0.975$; $\chi^2_2 = 0.159$, $p_2 = 0.690$	$\chi^2 = 4.248$, $p = 0.120$
	C/T	48.8	52.4		
	C/C	17.4	33.3		
	T	58.1	40.5		$\chi^2 = 4.250$, $p = 0.039$
	C	41.9	59.5		

Note: Numbers 1 and 2 in subscript represent group of remitters and group of non-remitters, respectively.

The present study reports association of remission following pharmacological antidepressant treatment with allele T of rs334558, but a previous study reported that this allele is associated with resistance to antidepressant medication[53] and others reported association of this allele with poorer response to lithium treatment.[54–56] In all these studies, contribution of other molecular factors, including different genetic and epigenetic backgrounds, was not taken account of. Treatment-resistant depression is a phenomenon far from being fully understood, with multiple molecular factors likely contributing to its development.[2,65,66] Different genetic and epigenetic backgrounds may modulate the influence of rs334558 on the response to drug treatment. In particular, the genetic landscape in different human populations could explain the changing direction of association depending on the population studied. In fact, allele frequencies of this functional variant change drastically in different human populations: according to data in the 1000 Genomes Project, the frequency of allele T goes from 67.1% in populations with European ancestry to 5.9% in populations with African ancestry (https://www.ncbi.nlm.nih.gov/projects/SNP/snp_ss.cgi?ss=ss1305845106). This may mean that different genetic factors interact with this functional variant in different human populations. It is thus possible that in our cohort a different genetic and/or epigenetic background defines the different outcome in the presence of allele T, namely remission following pharmacological treatment. Further examples of extensively investigated functional candidate genes, whose association with mental disorders and treatment response changes in different populations, are the brain-derived neurotrophic factor, encoded by *BDNF*,[67] and the serotonin transporter, encoded by *SLC6A4*.[68]

Because drug treatment of depressive disorders, due to their extensive heterogeneity, seems to be better viewed from the standpoint of personalized medicine, it is important to define actionable molecular biomarkers that will help predict treatment response.[10–19] The functional variant rs334558 could be such a genetic and pharmacogenetic biomarker for a number of phenotypes, including mood disorders, schizophrenia and neurodegenerative disorders. This biomarker could eventually be used in clinical settings, together with other relevant multidimensional data, such as levels of *GSK3B*'s promoter methylation or levels of expression of downstream targets of this gene, analyzed by machine-learning algorithms,[69–71] in order to determine the precise molecular etiopathological processes and recommend the appropriate personalized medicine-driven treatment.[27,72–75]

It is important to note that the personalized medicine approach, in the context of treatment of depressive disorders in particular, will be substantially complex because the task of determining actionable biomarkers will require an important volume of functional studies referring to treatment response. Multiplex functional studies[76] should be the most appropriate way to proceed, given the substantial volume of data involved. In addition, personalized medicine applications in clinic, including pharmacogenetic testing, have not yet been convincingly shown to be cost-effective,[73,74] so more prospective studies evaluating cost-effectiveness and development of new cost-effective treatment schemes are needed.

Conclusion

This study reported data, suggesting the role of the functional variant rs334558 as a pharmacogenetic biomarker for depressive disorders in the context of personalized medicine-driven treatment. The results of genotyping should be used in conjunction with other relevant biomarkers because the phenotypic outcome in the case of this potential biomarker depends on other genetic and epigenetic factors that modulate it.

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Disclosure

The authors report no conflicts of interest in this work.

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