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SLC6A4 Polymorphisms and Age of Onset in Late-life Depression on Treatment Outcomes with Citalopram: A Sequenced Treatment Alternatives to Relieve Depression (STAR*D) report

Paulo R. Shiroma^{1,†}, Maureen S. Drews², Jennifer R. Geske³, and David A. Mrazek²

¹Geriatric Psychiatry Clinic, Mental Health Service Line, Minneapolis VA Medical Center, University of Minnesota Medical School, Minneapolis, MN, USA

²Department of Psychiatry & Psychology, Mayo Clinic, Rochester, MN, USA

³Department of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, USA

Abstract

Objective—Age at onset of first major depressive episode (MDE) does not necessarily translate into different treatment outcomes to antidepressants in late-life depression. The influence of genetic variants may affect this relationship.

Design—Post-hoc dataset analysis of the association between variants in the promoter region (indel, rs25531) and within intron 2 (Stin2 VNTR) of the *SLC6A4* gene and treatment outcomes among older participants in the first treatment arm of the Sequenced Treatment Alternatives to Relieve Depression trial (STAR*D).

Setting—Participants were enrolled from 23 psychiatric and 18 primary care settings.

Participants—Two hundred twenty one, white-non Hispanic subjects, aged 60 to 75 years, with 16-item Quick Inventory of Depressive Symptomatology-Clinician Rating (QIDS-CR₁₆) initial score ≥ 10 , and who remained in the study for at least 6 weeks were genotyped.

Intervention—Citalopram treatment for up to 14 weeks

Measurements—Main outcome was remission rate defined as a score of ≤ 5 on the QIDS-CR₁₆. Response was a secondary outcome defined as a reduction of $\geq 50\%$ of baseline QIDS-CR₁₆.

Results—Polymorphism in the indel promoter region was associated with remission among subjects whose first lifetime episode of major depression occurred later than age 55. In this group, subjects with L/L genotype had significantly higher remission (80% vs. 43%) as compared to those subjects with any other indel promoter genotype. Multivariate analysis demonstrated that the genetic effect of the indel promoter region on remission increases along with age at onset of MDE.

Conclusions—Variants in the indel promoter region of *SLC6A4* gene have a more robust effect to antidepressant outcome among older subjects who experienced their first MDE at a later age. The mechanism of action of these variants remains to be determined.

[†]Author for correspondence: Tel.: +1 612 467 2264, Fax: +1 612 467 4010, paulo.shiroma@va.gov.

Keywords

depression; citalopram; Sequenced Treatment Alternatives to Relieve Depression (STAR*D); *SLC6A4*

Background

Studies on geriatric depression suggest that the age at onset of first major depressive episode (MDE) may correspond to clinical entities with different underlying etiology and presentation. Older patients whose first lifetime episode of depression occurs early in life have an increased genetic liability, recurrent depressive episodes, and decreased personal and psychosocial resources¹. In contrast, later age-of-onset depression tends to be heterogeneous in clinical presentation, with prominent medical comorbidities (e.g. cerebrovascular and degenerative diseases), with greater cognitive impairment and disability, and higher relapse². These differences, however, do not necessarily translate into different treatment outcomes to antidepressants.

Studies found that patients who experienced their first lifetime episode of major depression before age 60 take longer to achieve remission¹³ while other studies showed slower recovery among those who experienced their first episode of depression at older age⁴⁵. Moreover, subjects with recurrent lifetime depression after age 60, compared to those with a single episode, appears to take longer to respond to treatment⁶. Self-reported age at onset of the first MDE were also found to be unrelated to antidepressant treatment⁷⁸ including a study based on the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) sample⁹.

One objective of pharmacogenomic testing is to identify subjects who will respond to specific medication. Polymorphisms in the serotonin transporter solute carrier family 6, member 4 (*SLC6A4*) predicting treatment outcomes have been extensively studied¹⁰ but only limited data exist in elderly population¹¹. The most studied polymorphism in the *SLC6A4* gene is the indel promoter region (5-HTTLPR or SERT). Reports in the elderly found that carriers of the higher expression L/L genotype may respond both at lower antidepressant concentrations and at faster rate than those individuals with the lower function S allele¹²¹³.

Triallelic 5-HTTLPR locus with two subtypes of the long allele have been described¹⁴. The long variant with an adenosine at SNP 25531 (*L_A*) has been reported to have higher activity than the long variant with guanine at rs25531 (*L_G*)¹⁵. Subjects with the S or *L_G* alleles were reported to experience more adverse effects to citalopram compared to *L_A* allele carriers¹⁶ however, no evidence of association with remission or response were found¹⁷¹⁶. Contrary to the results of Hu et al., Mrazek and colleagues found that *L_G* haplotypes did not show effects similar to haplotypes carrying the S indel promoter allele. The regulatory role of the variable number of tandem repeats in the second intron of the *SLC6A4* gene (Stin2 VNTR) was demonstrated analyzing the STAR*D sample¹⁷. In this report, white non-Hispanic subjects with a copy of the short allele (9 repeats) and the 12-repeat allele had a remission rate of 70.6% compared to 48.7% for those subjects with any other genotype.

This study analyzes a genotyped sub-sample of geriatric (60 to 75 years old) depressed subjects treated with the selective serotonin transporter inhibitor (SSRI) citalopram in the first treatment arm of STAR*D trial. It tests the hypothesis whether variants in the promoter region (indel promoter, rs25531) and within intron 2 (Stin2 VNTR) of the *SCL6A4* gene moderate the association between age at onset of first MDE and antidepressant outcomes.

Methods

Study design and subjects

Post-hoc dataset analysis was conducted among participants treated with citalopram in the STAR*D trial. The rationale, methods, and design of the STAR*D study have been detailed elsewhere¹⁸¹⁹. Briefly, 4041 outpatient subjects between 18 to 75 years of age with non-psychotic major depression were enrolled from 23 psychiatric and 18 primary care settings. Severity of depressive symptoms was determined by baseline score of 14 of the 17-item Hamilton Rating Scale for Depression (HDRS). Exclusion criteria were bipolar disorder, psychosis, obsessive-compulsive disorder, or eating disorder; pregnancy, intending to conceive or breast feeding; unstable medical condition; substance dependence requiring inpatient detoxification; history of non response or intolerance in the current MDE to any protocol antidepressant in the first two treatment steps.

Citalopram was started at 20 mg/day up to an optimal target dose at 60 mg/day by week 6; however, flexible dosages was permitted based on tolerability and clinical response for up to 14 weeks including initiation of citalopram at <20 mg/day or a slower dose escalation.

Genotyped STAR*D sample

Our analyses of the STAR*D sample were approved by the Mayo Clinic Institutional Review Board. All participants provided informed consent. Blood samples were collected from 1953 of the 4041 enrolled subjects. After excluding subjects due to missing or discrepant genetic data, the analyses was conducted among participants aged 60 to 75 years at the study entry, self-reported as white-non Hispanic, and who showed evident depression at the time of enrollment indicated by 16-item Quick Inventory of Depressive Symptomatology-Clinician Rating (QIDS-CR₁₆) initial score 10. Subjects also remained in the study for at least 6 weeks, and adhered with the medication regimen based on a global rating of compliance.

For the analyses, the sample was dichotomized by age of onset of the first MDE based on patients' self-report. An a priori threshold age of 55 similar to that used in a previous publication using the STAR*D sample was chosen⁹. Groups were defined as having a first lifetime episode of major depression at age 55 or earlier versus first MDE at age 56 or later. The rationale for this arbitrary age cutoffs is based on the leading hypothesis for etiologic differences between the two groups that relates to brain vascular pathology. The prevalence of cerebrovascular events reported in the literature increases in the range of 50 to 60 years old²⁰²¹.

Outcomes measures

The analyses reported here focus on the remission of depression, as this is the primary goal of treatment. Response of depression is reported as a secondary outcome. Remission was defined as a score of ≤ 5 on the QIDS-CR₁₆ at the last clinic visit. A reduction of $\geq 50\%$ of baseline QIDS-CR₁₆ was used to define response rate. Outcomes were collected at 6, 9, and 12 weeks.

Statistical analysis

Means and standard deviations were used to describe continuous data and percentages for categorical variables. The baseline differences in demographic and clinical characteristics between groups (age-of-onset depression ≤ 55 vs. >55) were compared by using Student's *t* test or Mann-Whitney two-sample test for continuous variables, and χ^2 test statistics for categorical variables. Allele and genotype frequencies were compared between groups using χ^2 test or Fisher's exact test for rare alleles. Chi-square tests of Hardy-Weinberg Equilibrium were carried out for all genetic variants. Remission and response rates were compared across the three *SLC6A4* genetic variants of primary interest genotypes within each age-at-onset group using Fisher's exact tests. Logistic regression models were used to test for an interaction between each genetic variant and age-at-onset on remission after adjusting for the significant covariates. For these models, the indel promoter and intron 2 were coded additively as 0, 1, or 2 counts of S or 12, respectively. The rs25531 variant was dominantly coded comparing A/A to A/G and G/G combined because there was only 1 G/G in the sample.

Results

Demographic and clinical characteristics of the study sample are presented in Table 1. Subjects with onset of MDE >55 were older, less depressed at baseline as measured by QIDS-CR₁₆, and had lower daily dose of citalopram at study exit. The age onset of MDE between groups was significantly different. Subjects with onset of MDE >55 as compared to those onset of MDE ≤ 55 did not differ in rates of remission (55.8% vs. 47.8%) or response (61.2% vs. 58.2%). In the same vein, groups were not significantly different in gender distribution, family history of mood disorder, duration of current depressive episode, severity of depression at study exit, number and severity of comorbid medical conditions, or presence of anxiety.

Valid genotypes were obtained for the VNTR variation in the second intron of *SLC6A4* for 216 subjects, for the indel promoter polymorphism for 221 subjects, and for the rs25531 SNP for 221 subjects. Deviations from Hardy-Weinberg Equilibrium (HWE) were assessed among white-non Hispanic subjects. For subjects with onset of MDE ≤ 55 , the intron 2 VNTR polymorphism and genotypes at the rs25531 SNP were conformed to HWE expectations; genotypes at the indel promoter polymorphism showed some deviation from HWE ($\chi^2=4.39$, $df=1$, $p=0.04$). No deviations from HWE were detected for the three polymorphisms in the late-onset group.

The genotype distribution of the three polymorphic sites compared by the age of first MDE is summarized in Table 2. Significant variation between groups were observed for the intron 2 VNTR ($X^2=9.62$, $df=4$, $p=0.05$). There was no statistically significant association with first MDE for the indel promoter ($X^2=1.62$, $df=2$, $p=0.45$) or rs25531 SNP ($X^2=0.68$, $df=2$, $p=0.71$).

For the whole sample, genetic variants for the indel promoter, rs25531, and intron 2 VNTR had no significant association with remission ($X^2=4.51$, $df=2$, $p=0.10$; Fisher's exact tests: $p=0.92$; $p=0.46$, respectively) or response ($X^2=5.42$, $df=2$, $p=0.07$; Fisher's exact test, $p=0.90$; $X^2=2.20$, $df=4$, $p=0.69$, respectively). Table 3 showed the association between the three polymorphic sites and the occurrence of remission for each age group. Pair-wise comparisons were performed for each genotype to the remaining pooled genotypes with Bonferroni correction applied to p-values for multiple comparisons (adjusted p-values).

Among depressed subjects with first time MDE at 56 or later, the indel promoter polymorphism was associated with remission (Table 3) and response ($X^2=6.63$, $df=2$, $p=0.036$). Pair-wise comparison of genotypes in the indel promoter showed that subjects carrying the L/L genotype had a remission rate of 80% as compared to 43% of the subjects with remaining genotypes ($p=0.03$, adjusted $p=0.05$, Fisher's exact test). Response rate between L/L carriers to those subjects with any other indel promoter genotype was similar to remission rates (80% versus 44.4%, $p=0.05$, adjusted $p=0.21$, Fisher's exact test). There were no statistically significant associations between genotypes at rs25531 SNP and intron 2 VNTR with the rates of remission or response. Among subjects with onset of depression at age 55 or earlier, the three polymorphic sites were not significantly different in the rates of remission or response (data not shown).

Table 4 showed multivariate logistic regression models for only remission of depression, as this is the primary goal of treatment. Independent effect of age, age at onset of MDE, genetic variant, and an interaction term of the variant and age of onset were included as predictors in each model. Age of onset was treated both as a dichotomous and as a continuous variable. The dichotomization of age at onset of MDE produces easily understandable results and facilitates the study of interaction effects. On the other hand, analyses of age of onset as a continuous variable decrease the likelihood to lose information between variables because of dichotomization. Analyses demonstrated that the interaction of the indel promoter with age-at-onset dichotomous group was only marginally significant. Interactions between age-at-onset and either rs25531 or Intron 2 were not statistically significant.

When age-at-onset was entered into the model as continuous variable, results were similar but variants in the indel promoter region significantly affect remission after adjusted for age and age-at-onset. Older age was associated with increased probability of remission ($OR=1.08$, $p\text{-value}=0.007$). There was also significant interaction between the indel promoter variant and age-at-onset (Table 4), meaning the effect of the indel promoter variant on remission is different by age-at-onset. Specifically, remitters with the L/L genotype had later age of onset than non-remitters of the same genotype (means: 40.8 vs. 27.8 years), remitters with the L/S genotype were of similar age of onset compared to non-remitters of the same genotype, (means: 35.7 vs. 35.8 years), and remitters with the S/S genotype had

earlier age of onset compared to non-remitters of the same genotype (means: 25.8 vs. 37.8 years). Therefore, we see a consistent effect of age on remission, but the effect of age-at-onset of MDE interacts with genotype in relationship to remission. Figure 1 displays the interaction of age of onset and genotype for the mean age of the sample (61 years old).

Exploratory analyses were conducted on the joint effects of the three candidate polymorphisms over remission for subjects with a later onset of first MDE. For the promoter region (indel, rs25531), carriers of L_A/L_A genotype had a remission rate of 77% as compared to 46% for those with remaining genotypes, however this association was not statistically significant ($p=0.09$, Fisher's exact test). Further analysis combine the effect of the intron 2 VNTR variants to the indel promoter region. It was hypothesized that subjects homozygous for the L_A allele or with one copy of the L_A allele and one copy of the VNTR 12 allele would have a “more active” gene expression as compared to “less active” subjects with any other genotype. Thus, the more active subgroup achieved a remission rate of 65% while those subjects with any other *SLC6A4* genotype had a remission rate of 20% ($p=0.02$, Fisher's exact test). Similar exploratory analyses conducted in the early onset group showed non-significant association of the combined effect of the three candidate polymorphisms and remission ($X^2=0.52$, $df=1$, $p=0.59$).

Discussion

In a STAR*D report, Kozel and colleagues found lack of significant association between earlier versus late onset of first depressive episode and treatment outcomes in older depressed patients⁹. By using similar age criteria, the current study found only marginally significant interaction between polymorphism of the indel promoter region of the *SLC6A4* and age-of-onset groups on rates of remission to citalopram. However, analyses of age of onset of MDE as a continuous variable demonstrated that variants of the indel promoter region had a more robust effect on remission with later onset depression. This finding is supported by a recent meta-analysis²² which revealed that L/L genotype compared to S carriers has increasing probability of response as age at onset of depression increases. Although exploratory, the study also found a “higher active” group for the serotonin transporter consisting of carriers of higher expression L_A/L_A genotype and those with L_A -12 alleles combination were most strongly associated with remission to citalopram. These results suggest that 12 VNTR allele may contribute to enhance effect of the indel promoter L allele but only among those with late-onset depression.

The distribution of intron 2 VNTR variants was associated with onset of MDE. The VNTR region within intron 2 is transcriptional regulatory domain where the nine copy allele appears to have a higher level of expression than the 10- or 12-copy VNTR alleles. Efforts to identify potential contribution of this with affective disorder have yielded mixed results. A meta-analysis found no involvement of the intron 2 VNTR in unipolar or bipolar depression²³; however, an analysis of haplotype distribution with variants in the indel promoter region showed increased frequency of S-10-repeat VNTR allele in major depression with melancholia²⁴. The presence of 10-repeat VNTR allele and the absence of 12-repeat VNTR allele was also related to cognitive dysfunction detected in major depression²⁵.

The serotonin transporter is the principal site of action of SSRIs. The genetic variation at the *SLC6A4* gene was involved in the vulnerability to depression and response to antidepressants¹²²⁶. Limited studies in the elderly showed no significant effect of genotype in the final outcome (> 8 weeks) but rather association of S allele with a slower treatment response¹³. Given modest genetic effect sizes of *SLC6A4* genetic variation and response to SSRIs²⁷, small sample sizes in previous studies may have been underpowered to detect positive associations. This study attempted to overcome that limitation by including a larger numbers of older subjects. The analyses were also exclusively conducted in white non-Hispanic subjects minimizing the chances of spurious associations due to the inclusion of samples of diverse ancestral origin. Our analysis categorized subjects as remitters if they remained in remission at study exit excluding those who may have achieved temporary remission but who subsequently developed higher depression scores.

The exact mechanisms by which polymorphism influence outcomes to SSRIs in the later age-of-onset group with depression remain unclear but likely multiple factors intertwine. Depressive disorders, particularly in the elderly, are associated with diminished serotonergic function²⁸. Similarly, the S allele has been associated with relatively lower serotonin function than the L allele²⁹. Functional studies of serotonin systems measured by cerebral metabolic response to a serotonergic challenge showed greater decreases in left cortical structures among both depressed geriatric patients and S-allele carriers, possibly as a compensatory mechanism to relatively decreased serotonin function³⁰³¹³². Thus, a deficiency in serotonin could represent a neurobiological substrate with genetic explanation for the differential response to antidepressant drugs in the elderly.

Evidence from the vascular depression hypothesis³³ suggests greater prevalence of brain vascular pathology in patients with depressive disorder commencing later in life (aged 50 or over)³⁴. The hypothesis posits that subcortical structures involved in mood regulation and white matter pathways may become disconnected from structures in the frontal cortex²⁰³⁵ with greater severity of white matter lesions associated to poor antidepressant response³⁶²⁰.

A recent report by Alexopoulos and colleagues³⁷ found that elderly depressed S-allele carriers had more microstructural white matter abnormalities in the fronto-limbic system and lower remission rates than L-allele carriers. The presence of SL-allele status was associated with increased cholesterol, triglycerides, and risk for heart disease, angina and heart attacks in individuals aged 50-70 years³⁸. Moreover, S-allele carriers had a higher probability of cardiac events after an acute myocardial infarction including cardiac death, revascularization, heart failure, reinfarction, arrhythmia, and unstable angina than L homozygotes³⁹. The presence of S allele, therefore, may compromise cerebrovascular integrity by disrupting cortical-subcortical connections that complicate attempts to re-establish neurochemical balance using antidepressants. In contrast to S-allele higher risk of vascular depression, LL genotype was associated with greater platelet activation⁴⁰ and with greater increase in heart rate and blood pressure in response to stress⁴¹, both risk factors for the development of subcortical ischemic disease commonly seen in late-life depression.

The occurrence of depression in the absence of vascular risk factors⁴² suggests that other mechanisms may also be involved in the role of serotonin transporter gene and the response

to antidepressants in the elderly. Glucocorticoids modulation by the serotonin system⁴³ and differential susceptibility to glucocorticoids associated in serotonin transporter expression⁴⁴ may result in increased vulnerability to depressive symptoms triggered by age-related stressful life events such as bereavement and medical illness, and the reduced response in serotonin neurotransmission among S allele carriers. The S allele was also associated with a reduced brain-derived neurotrophic factor (BDNF) modulation of serotonin function in lymphoblasts⁴⁵ which could interfere with the antidepressants effect of promoting neurogenesis⁴⁶.

The degree of susceptibility to the potential neurotoxic effects of stress may be mediated by genetic variations in the indel region of serotonin transporter gene and could be related to degenerative changes in brain structures relevant to depression later in life. In a post-hoc analysis, Taylor and colleagues found smaller hippocampal volumes associated with both L/L genotype in late-onset depression and SS genotype in early onset depression²¹. Smaller hippocampal volumes were associated with poorer antidepressant response in geriatric depression⁴⁷. The hyperactivation of amygdala⁴⁸ in response to fearful stimuli among S-allele carriers with the ventromedial prefrontal cortex as a compensatory mechanism⁴⁹ also constitute another path of cortical-subcortical dysregulation which could interfere with response to antidepressants.

There are several limitations to consider in the interpretation of the study. The number of subjects with later onset of first MDE is small for which results should be confirmed by larger samples. The generalizability of results was limited by excluding participants older than 75 years of age who may have had greater medical comorbidity and possibly different outcomes. Similarly, the exclusion of participants unsuccessfully treated with citalopram in the past and the analyses performed on subset of patients that completed at least 6 weeks of treatment would identify subjects with better clinical outcomes than those obtained in the general population. The lack of a placebo group in the design of STAR*D does not allow clinical outcomes to be analyzed within the context of other factors that could have influenced remission. Of interest, subjects with the long allele in the indel promoter region have been reported to be more responsive to placebo⁵⁰ which may have had a differential effect on the two groups. The cut-off age to define onset of depression is somewhat arbitrary and the ascertainment of age of onset was obtained by self-report. There was a wide range distribution in the age of onset among the early-onset group (interquartile range between 18 to 42 year-old) as compared to the late-onset group (interquartile range between 60 and 68 year-old). Finally, potential confounders such as medication use prior to study entry, concomitant medication use, medication compliance were not strictly monitored.

In conclusion, variants in the indel promoter region of *SLC6A4* gene have a more robust effect to antidepressant outcome among older subjects who experienced their first MDE at a later age. The mechanism of action of these variants remains to be elucidated.

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Figure 1.

Probability of remission for sample mean age of 61 years old varies by the interaction between variants in the indel promoter region of *SLC6A4* gene and age of onset of major depressive episode (MDE).

Table 1
Demographic and clinical characteristics by age-of-onset of MDE among older subjects in the STAR*D study sample

Characteristics	Onset of MDE 55 N=178	Onset of MDE>55 N=43	Test Statistics
Age (years), mean (S.D.)	60.2 (5.3)	64.2 (4.9)	$t=4.57$, $df=219$, $p<0.001$
Age (years) at first MDE, median (interquartile range)	28 (18 to 42)	64 (60 to 68)	<i>Mann-Whitney U test</i> , $Z=10.2$, $p<0.001$
Gender, N°			
Male	84	22	$X^2=0.22$,
Female	94	21	$df=1$, $p=0.640$
Family history of mood disorder, N°			
Yes	92	21	$X^2=0.11$,
No	86	22	$df=1$, $p=0.737$
Duration of current episode (months), mean (S.D.)	37.3 (73.7)	20.0 (26.9)	$t=1.517$, $df=219$, $p<0.001$
QIDS-CR ₁₆ remission, N°			
Yes	85	24	$X^2=0.90$,
No	93	19	$df=1$, $p=0.343$
QIDS-CR ₁₆ response, N°			
Yes	109	25	$X^2=0.139$,
No	69	18	$df=1$, $p=0.709$
Base QIDS-CR ₁₆ , mean(S.D.)	16.2 (3.3)	14.9 (3.2)	$t=2.16$, $df=219$, $p=0.021$
Exit QIDS-CR ₁₆ ,mean(S.D.)	7.7 (5.3)	7.4 (5.4)	$t=0.33$, $df=219$, $p=0.740$
Maximum dose of citalopram at study exit (mg/day), mean (S.D.)	47.3 (14.8)	41.7 (18.1)	$t=2.13$, $df=219$, <0.03
Chronic Illness Ratings Scale (CIRS)			
Category, mean (S.D.).	4.5 (2.4)	4.6 (2.6)	$t=0.24$, $df=219$, $p=0.809$
Total, mean(S.D.)	6.9 (4.2)	7.3 (5.1)	$t=0.53$, $df=219$, $p=0.592$
Severity, mean(S.D.)	1.4 (0.5)	1.4 (0.5)	$t=0$, $df=219$, $p=1.000$
Anxiety, N°			
Yes	28	3	$X^2=2.00$,

Characteristics	Onset of MDE 55	Onset of MDE>55	Test Statistics
	N=178	N=43	
No	148	38	$df=1$, $p=0.157$

Abbreviations: MDE, major depressive episode; QIDS-C16, 16-item Quick Inventory of Depressive Symptomatology–Clinician Rated; STAR*D, Sequenced Treatment Alternatives to Relieve Depression.

Table 2
Distribution of genotype variation by age-of-onset of MDE among older subjects in the STAR*D study sample

	Onset of MDE ≤55	Onset of MDE >55
Intron 2 VNTR, N°		
9/10	1	3
9/12	6	--
10/10	27	7
10/12	76	16
12/12	64	16
Indel promoter, N°		
L/L	57	15
L/S	99	20
S/S	22	8
rs25531, N°		
A/A	154	39
A/G	23	4
G/G	1	--

Abbreviations: MDE, major depressive episode; VNTR, variable number of tandem repeats; L, long; S, short; A, adenosine; G, guanine.

Table 3
Genotype association to remission^a phenotypes by first onset of MDE among depressed elderly in the STAR*D study sample

		Onset of MDE 55 (N=178)			Onset of MDE>55 (N=43)		
		N	% Remitted	P-value*	N	% Remitted	P-value*
Indel promoter							
	L/L	57	52.6	0.635	15	80.0	0.034
	L/S	99	46.5		20	50.0	
	S/S	22	40.9		8	25.0	
rs25531							
	A/A	154	48.1	0.656	39	53.9	0.618
	A/G	23	43.5		4	75.0	
	G/G	1	100.0		0	-	
Intron 2 VNTR							
	9/10	1	0.0	0.437	3	100.0	0.501
	9/12	6	83.3		0	-	
	10/10	27	48.2		7	57.1	
	10/12	76	47.4		16	56.3	
	12/12	64	46.9		16	50.0	

^a Defined by the 16-item Quick Inventory of Depressive Symptomatology–Clinician Rated.

^{*} P-value from Fisher's exact test

Abbreviations: MDE, major depressive episode; VNTR, variable number of tandem repeats; L, long; S, short; A, adenosine; G, guanine; STAR*D, Sequenced Treatment Alternatives to Relieve Depression

Table 4

Multivariate models (with age adjustment) for interactions between genetic variant and age of MDE onset.

Variable	P-values [‡]		
	Indel promoter	rs25531	Intron 2 VNTR
Age	0.007	0.008	0.012
Age of MDE onset (years)	0.007	0.963	0.308
Genetic variant	0.068	0.328	0.466
Age of MDE onset * Genetic variant	0.002	0.196	0.374
Age	0.009	0.002	0.050
Age of MDE onset (≤ 55 or >55 years old)	0.131	0.008	0.014
Genetic variant	0.014	0.924	0.423
Age of MDE onset * Genetic variant	0.067	0.506	0.412

Abbreviations: MDE, major depressive episode; VNTR, variable number of tandem repeats; L, long; S, short; A, adenosine; G, guanine.

[‡]P-values from Wald chi-square, df = 1.