Published in final edited form as:

Psychosom Med. 2008 November ; 70(9): 953–959. doi:10.1097/PSY.0b013e318187aee6.

Relationship of Genetic Variability and Depressive Symptoms to Adverse Events After Coronary Artery Bypass Graft Surgery

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Abstract

Objective—To assess genetic variability in two serotonin-related gene polymorphisms (MAOA-uVNTR and 5HTTLPR) and their relationships to depression and adverse cardiac events in a sample of patients undergoing coronary artery bypass surgery.

Methods—A total of 427 coronary artery bypass graft (CABG) patients were genotyped for two polymorphisms and assessed for depressive symptoms at three time points, in accordance with the Center for Epidemiological Studies-Depression (CES-D): preoperative baseline; 6 months postoperative; and 1 year postoperative. Logistic regression was used to assess the association between depressive symptoms (CES-D = >16), genotype differences, and cardiac events. Because MAOA-uVNTR is sex-linked, males and females were analyzed separately for this polymorphism; sexes were combined for the 5HTTLPR analysis.

Results—Depressed patients were more likely than nondepressed patients to have a new cardiac event within 2 years of surgery ($p < .0001$); depressed patients who carry the long (L) allele of the 5HTTLPR polymorphism were more likely than the short/short (S/S) carriers to have an event ($p = .0002$). Genetic associations with 6-month and 1-year postoperative depressive symptoms do not survive adjustment for baseline depressive symptoms.

Conclusions—A serotonin-related gene polymorphism—5HTTLPR—was associated with adverse cardiac events post CABG, in combination with depressive symptoms. Because depressed patients with the L allele of the 5HTTLPR polymorphism were more likely to have an event compared with the S/S carriers, combining genetic and psychiatric profiling may prove useful in identifying patients at the highest risk for adverse outcomes post CABG.

Keywords

depression; CABG surgery; serotonin; genetic variability; monoamine oxidase-A; serotonin transporter gene

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Introduction

Research over the past two decades has shown strong associations between depression and cardiac health. Depression is now known to be an independent risk factor for coronary artery disease (CAD) (1), and can be a precursor to myocardial infarction (MI) (2) and even cardiac death (3). After an acute MI, patients who are depressed are at increased risk for mortality, (4) experience a greater likelihood of cardiac hospitalization, and suffer from poor quality of life in the first year post MI (5).

Coronary artery bypass grafting (CABG) is a common surgical intervention for CAD patients, and the incidence of depression is high before and after surgery; pre- and postsurgical depression estimates range between 14% and 47% (6–8). Depression on the day before surgery as well as depression that persists until 6 months after surgery is associated with a two- to three-fold increased risk of mortality. Even patients who are mildly depressed 6 months after coronary artery bypass surgery are more likely to die (9). Depressed patients are more than twice as likely as nondepressed patients to have a cardiac event within 12 months after surgery (9). Furthermore, patients who were not depressed before surgery but who developed new-onset symptoms within 6 months of surgery are at higher risk than nondepressed patients for long-term cardiovascular events and death from cardiovascular causes (9–11).

Variation in serotonin metabolism has been implicated in multiple mood disorders, including depression. Genetic variability in two serotonin-related polymorphisms, in turn, has been linked to alterations in serotonin levels (10). MAOA-uVNTR is a polymorphism in the upstream regulatory (promoter) region of the gene encoding for monoamine oxidase A (MAOA), which deaminates serotonin and norepinephrine (11). It consists of a 30 base pair repeated sequence and presents as a variable number of tandem repeats (VNTR), wherein alleles with 3.5 or 4 copies of the repeat sequence are transcribed two to ten times more efficiently (11). The 5HTTLPR is a 44 base pair insertion/deletion polymorphism in the 5' flanking regulatory region of the serotonin transporter gene, characterized by either long (L) or short (S) alleles, that is associated with differential transcriptional efficiencies (12). Reduced serotonin transporter transcription, expression, and function have been reported in S allele carriers than in L allele homozygotes (13). Both polymorphisms also have been associated with variation in central nervous system serotonin turnover (10,14). Because serotonin levels are modulated by these two polymorphisms, we hypothesized that genetic variability in MAOA-uVNTR and 5HTTLPR is associated with postoperative depressive symptoms in CABG surgery patients. In addition, we sought to confirm and extend previous findings by determining if genetic markers moderate the relationship between elevated depressive symptoms and greater adverse events in post-CABG patients.

Methods

Study Sample

Patients enrolled in this study were part of the Perioperative Genetics and Safety Outcomes Study (PEGASUS), an ongoing Institutional Review Board approved, prospective, longitudinal study at Duke University Medical Center. The current substudy targeted a cohort of patients, undergoing isolated CABG surgery utilizing cardiopulmonary bypass (CPB) between September 1993 and June 2002, in whom depression had been evaluated preoperatively and again at 6 months and 1 year after surgery.

All patients included in the current study were selected from a cohort of subjects prospectively enrolled in trials assessing neurocognitive function after cardiac surgery. Patients were excluded from enrollment into these trials if they had active liver disease, renal failure (creatinine of >2 mg/dl), history of stroke with residual deficit, inability to read, less than

seventh grade education, any Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) diagnosis, and active treatment for a psychiatric disorder including depression. Patients with any past or current DSM-IV diagnoses, noted from either chart review or history and physical interview by a member of the investigative team, were excluded because of the potential confounding effect on postoperative cognition.

Patient Management

Anesthesia was induced and maintained with midazolam, fentanyl, and isoflurane. All patients underwent nonpulsatile hypothermic (30°C–32°C) CPB. The perfusion apparatus consisted of a membrane oxygenator (CML, COBE Chem Labs, Lakewood, Colorado), pump (Sarns 7000 MDX, 3 M Inc., Ann Arbor, Michigan), and arterial line filter (SP3840, Pall Biomedical Products Co., Glen Cove, New York). Perfusion was maintained at pump flow rates of 2 to 2.4 L × min⁻¹ × m² throughout CPB. The pump was primed with crystalloid, and serial hematocrit levels were kept at ≥0.18 with packed red blood cell transfusion as necessary. Arterial blood gases were measured every 15 to 30 minutes to maintain arterial carbon dioxide partial pressures of 35 to 40 mm Hg, unadjusted for temperature (α-stat), and oxygen partial pressures of 150 to 250 mm Hg.

Assessment of Depression

On the day before surgery, and at 6 months and 1 year after surgery, patients completed the 20-item Center for Epidemiological Studies Depression (CES-D) questionnaire (15), rating the degree to which they experienced a range of symptoms of depression such as “I had crying spells,” “I felt lonely,” and “I was bothered by things that usually don't bother me.” Items are rated on a 4-point Likert scale and summed for a total score. Scores range from 0 to 60 with higher scores indicating greater depressive symptoms. As in our previous work (9), a score of <16 on the CES-D defined patients as having no depressive symptoms; mild depressive symptoms were defined by a CES-D score of 16 to 26; and severe depressive symptoms were defined by a CES-D score of ≥27.

Genotyping

Blood samples were collected into 3-ml Vacutainer (Becton Dickinson, Franklin Lakes, New Jersey) blood tubes containing 5.4 mg of K2 ethylenediaminetetraacetic acid (EDTA), and deoxyribonucleic acid (DNA) was isolated from lymphocytes using an AutoGen3000 automated platform for isolating genomic DNA from whole blood (AutoGen Inc., Cambridge, Massachusetts).

Genotyping to determine allele frequency of the 30bp VNTR mutation in the MAOA promoter region was carried out via polymerase chain reaction (PCR) using primers corresponding to nucleotide positions –1347 to –1367 (5'-ACAGCCTGACCGTGGAGAAG-3') and –1043 to –1024 (5'-GAACG-GACGCTCCATTCGGA-3') for the 3 repeat allele. Reaction conditions were 95°C for 5 minutes, followed by 35 cycles of denaturation at 95°C for 30 seconds, annealing at 62°C for 30 seconds, extension at 72°C for 1 minute, and finally 72°C for 10 minutes. PCR products were separated by running out on 3% agarose gels or 12% acrylamide gels containing ethidium bromide and visualized with ultraviolet light (UV). Repeat variants were confirmed via sequencing of PCR products from representative samples.

Genotyping of the insertion/deletion mutation in the serotonin transporter promoter region (5HTTLPR) was also carried out via PCR amplification to determine alleles containing either the short (475bp) or long (518bp) variant using primers corresponding to nucleotide positions –1406 to –1384 (5'-CTCT-GAATGCCAGCACCTAACCC-3') and –910 to –888 (5'-GAGGGACT-GAGCTGGACAACCAC-3'). Reaction conditions were 95°C for 5 minutes, followed by 40 cycles of denaturation at 95°C for 30 seconds, annealing at 62°C for 30 seconds,

extension at 72°C for 1 minute, and finally at 72°C for 10 minutes. PCR products were separated by running out on 2% agarose gels containing ethidium bromide and visualized with UV light. Because the serotonin transporter promoter region is GC rich, 7-Deaza-2'-dGTP was used in place of dGTP for PCR reactions. Short and long variants were confirmed via sequencing of PCR products from representative samples.

Statistical Analysis

Our primary analysis of the MAOA-uVNTR polymorphism compares patients with either of the two more efficient alleles (3.5 or 4 repeats) to those having only the less efficient 2, 3, or 5 repeat alleles, stratified by gender (14). Because males carry only one allele at each X chromosome locus, men will be hemizygous for the 3.5/4 versus 2/3/5 repeat alleles (16). Because females, with two X chromosomes, have the possibility of being heterozygotic, we employed a secondary analysis to examine the effects of MAOA-uVNTR among females, using three genotype categorizations: 3/3, 3/4, and 4/4. These three genotypes account for 94% of the sample. The remaining genotypes were not included because these groups were too small to yield any meaningful conclusion.

5HTTLPR is characterized by L and S alleles; analyses are based on three possible genotypes (L/L, L/S, and S/S). Because initial analyses showed no gender differences in genotype distribution, males and females were analyzed together; gender was included as a covariate in logistic regression models to account for gender differences in the incidence of depressive symptoms.

Depressive symptoms and genotype were examined as predictors of new cardiac events within 2 years of surgery. A cardiac event was defined as any of the following: repeat coronary revascularization (CABG surgery or percutaneous coronary intervention), MI, cardiac arrest, or all-cause mortality. The χ^2 tests and logistic regression models were used to examine this composite end point.

Postoperative depressive symptoms at 6-month and 1-year follow-up were also examined, with genotype as the main predictor of interest. Logistic regression employing age, gender, ethnicity, and baseline depressive symptoms as covariates was used to assess the relationship between genotype and postoperative depressive symptoms, defined as a binary variable (CESD ≥ 16). Several studies have shown that allele frequencies in serotonin related genes vary as a function of ethnicity (10,17). Therefore, self-identified race, which has been shown to account well for genetic cluster membership (18), was controlled for in the statistical modeling. Because our sample was 87% Caucasian, race was tested as a binary covariate (Caucasian versus non-Caucasian) in the analyses. Interactions between genotypes (MAOA-uVNTR, 5HTTLPR), genotype (MAOA-uVNTR, 5HTTLPR) and race, and genotype (5HTTLPR) and gender were also tested.

All analyses were conducted with SAS version 9.1; $p < .05$ was considered significant.

Results

A total of 1007 patients, who were enrolled in protocols assessing neurocognitive outcomes between September 1994 and May 2003, were genotyped for MAOA and the serotonin transporter polymorphism; of these, 658 had preoperative depression assessed as a part of the neurocognitive protocol. A total of 175 were excluded because they were undergoing surgery other than isolated CABG; 13 were excluded because they underwent surgery without CPB; 43 more were eliminated due to genotype error, for a sample size of 427 patients at baseline. Seven patients were lost to follow-up at 6 months and 16 patients were lost to follow-up at 1 year, leaving 420 and 411 evaluable patients, respectively.

A total of 128 (30%) patients of the baseline sample were female; 299 (70%) patients were male. Characteristics of the study population are shown in Table 1. Women undergoing CABG surgery were more likely to be older, non-Caucasian, hypertensive, diabetic, and received fewer bypass grafts, whereas men were more likely to have suffered a prior MI. Depressive symptoms were highly prevalent at the time of surgery; 28% of males ($n = 84$) and 57% of females ($n = 73$) had at least mild symptoms (CES-D >16) at baseline (Table 2). At 1 year after surgery, 17% of males and 32% of females showed depressive symptoms; 4% of males and 13% of females had moderate-to-severe depressive symptoms. Seven percent of males and 9% of females had new-onset depressive symptoms at 6 months; at 1 year, 10% of males and 6% of females showed new-onset depressive symptoms.

The incidence of cardiac events within 2 years of surgery was higher in patients with depressive symptoms compared with patients without depressive symptoms (19.0% versus 8.2%; $p < .0001$; odds ratio (OR) = 2.6; 95% Confidence Interval (CI) = 1.6–4.3) (Table 3). Although neither polymorphism was predictive of cardiac events as a main effect, there was a significant interaction between baseline depression and the 5HTTLPR genotype. Patients who had depressive symptoms at baseline and who carried the L allele were more likely than patients who did not carry the L allele to have a cardiac event ($p < .001$) (Figure 1). This finding persisted after adjusting for the Hannan score (a risk score incorporating comorbidities, age, and sex) (19).

MAOA allele frequencies were similar in males and females, and females were in Hardy-Weinberg equilibrium (the Hardy-Weinberg law describes genetic balance within a population with respect to homozygote and heterozygote frequencies). Eighty-three percent of females and 63% of males had an “efficient” allele (3.5, 4). MAOA genotypes were 14%, 43%, and 42% for genotypes 3/3, 3/4, and 4/4, respectively. In men, the frequencies were 36% and 64% for 3s and 4s, respectively. Race was not a significant predictor of depressive symptoms in women but was associated with depressive symptoms at 1 year in men, with non-Caucasian males having more symptoms than Caucasian males (41% versus 15%; $p = .003$). In the primary analysis, the efficient MAOA genotype (3.5/4) was not associated with a greater likelihood of depressive symptoms females at 6 months or 1 year ($p = .90$ and $p = .73$) after surgery. For males, the efficient genotype was associated with depressive symptoms at 6 months ($p = .02$; OR = 2.00; 95% CI = 1.13–3.51), but not at 1 year ($p = .55$). This 6-month finding, however, does not survive adjustment for baseline depression (MAOA, $p = .28$), suggesting that preoperative depression is the single best predictor of postoperative depression, despite genotype differences.

Secondary analysis, examining genotype effect among females only, revealed a significant effect of the 3/4 genotype, with heterozygotes showing almost twice the incidence of depressive symptoms, independent of age and race, as either of the homozygote genotypes at both 6 months (OR = 1.95; 95% CI = 1.03–3.76; $p = .04$) and 1 year (OR = 3.67; 95% CI = 1.68–8.36; $p = .001$). This significance does not survive adjustment for baseline depression, suggesting that genotype does not play a significant role in predicting postoperative depression independent of preoperative depression ($p = .58$ at 6 months; $p = .68$ at 1 year).

Although neither candidate polymorphism was significantly predictive of depressive symptoms at baseline (MAOA in males, $p = .06$; MAOA in females, $p = .43$; 5HTTLPR in combined gender group, $p = .06$), trends are evident that may be significant in larger samples.

Among women, the 5HTTLPR genotypes were 34%, 44%, and 22% for genotypes L/L, S/L, and S/S, respectively. In men, the genotypes were 35%, 46%, and 19% for genotypes L/L, S/L, S/S. The 5HTTLPR genotype distributions did not differ significantly between men and women ($p = .53$); therefore, the analyses were done combining both sexes and using all three

genotypes. Characterization of genotypes by the presence of one or two copies of the short allele (S/S and S/L), or no copies (L/L), adjusting for age, gender, and ethnicity revealed a significant association between postoperative depressive symptoms at 1 year and the L/L 5HTTLPR genotype ($p = .02$) and gender ($p = .003$), but not race ($p = .09$). No genotype association was found at 6 months ($p = .07$) (Table 4). No significant interactions were noted in these analyses.

Continuous Analyses

All analyses were repeated with the CESD considered as a continuous, rather than a categorical, outcome. All major findings were corroborated by these supportive analyses.

Discussion

Results from this prospective study indicate that CABG patients with elevated depressive symptoms are at greater risk for adverse cardiac events than patients without depressive symptoms. Specifically, we find that the presence of the 5HTTLPR L allele, in combination with baseline depression, is associated with an increased incidence of adverse cardiac events.

MAOA is a mitochondrial enzyme that preferentially deaminates serotonin and norepinephrine (11). The involvement of MAOA in behavioral disorders is highlighted by the use of MAOA inhibitors to treat depression and by the fact that transgenic adult male mice with a deletion of the MAOA gene demonstrate increased aggression (20). The MAOA gene sequence contains four exact repeats of a 30 base pair sequence located upstream to the transcription initiation site, which have been reported to be present as variants consisting of a variable number of tandem repeats (MAOA-uVNTR) (11). Alleles containing 3.5 or 4 repeats of the 30 base pair sequence are expressed significantly more efficiently (2.4- to 9.6-fold increases in gene transcription when compared with the 3 and 5 allele), suggesting that there is an optimal length for the repeat region to activate transcription (11).

The 3.5, 4, and 5 tandem repeats have been previously reported to predict major depression in females (21). Our findings support this observation in that we found that males with the 3.5 or 4 tandem repeats (efficient transcribers) are at greater risk for postoperative depressive symptoms. It is likely that this association in the efficient transcribers is a consequence of the higher levels of available MAOA, leading to greater intracellular catabolism of serotonin. However, genotype does not add significant predictive value beyond the information contained in preoperative depressive symptoms.

To our knowledge, the observation that females bearing the MAOA genotype 3/4 are at increased risk of depression relative to either 3/3 or 4/4 homozygote has not been reported previously. Based on transcriptional efficiency alone, we would expect expression of the MAOA gene in 3/4 females to fall between expression in 3/3 and 4/4 females. The phenomenon of X-chromosome inactivation in females, however, complicates a simple model of differential allele expression for MAOA. Because X-chromosome inactivation occurs in early embryogenesis (22), the extent of variation among heterozygotes in tissue mosaicism for MAOA allele expression is unknown and may be substantial. Moreover, approximately 15% of genes on inactive X chromosomes may be expressed (23). These features of X-chromosome inactivation and gene expression make our observation that 3/4 females are at increased risk of depression difficult to interpret in terms of transcriptional efficiency alone. Nevertheless, to the best of our knowledge, our report is the first to examine and report a relationship between MAOA genotype and depressive symptoms in females undergoing CABG surgery.

Serotonin has long been thought to modulate emotional states (13). The serotonin transporter plays an essential role in determining the duration and intensity of the serotonin communication

with its receptors on postsynaptic targets and with presynaptic receptors that exert inhibitory control over the serotonin neuron itself. The serotonin transporter polymorphism (5HTTLPR) encodes two allelic forms: a short (S), and a long (L); allelic frequencies vary substantially across populations (17). Although the S allele has been shown to be associated with less serotonin transporter transcription, expression, and function, reduced serotonin availability has not consistently been associated with the S allele (24). Prior studies have also provided conflicting data regarding associations with outcomes, with some studies reporting that the S allele was associated with depressive symptoms and increased risk of new cardiac events in MI patients (25–27), whereas others have indicated that the L/L genotype is associated with susceptibility to MI (28) and coronary heart disease (29). In our study, we found that the 5HTTLPR L/L genotype was associated with increased depressive symptoms 1 year after CABG surgery, and that the presence of the L allele, in combination with baseline depression, is associated with increased incidence of adverse cardiac events. Although the reasons for differing findings are not clear, there are several features of our sample that should be noted. First, we excluded patients who have a clinical diagnosis of major depression or who were being treated for depression preoperatively; although it is not immediately obvious what bias this exclusion might impose on our sample, it is important to acknowledge this potential limitation. Second, recent studies (30–33) suggested that multiple sources of epistasis (the effect of one gene on the function of another) exist that affect the regulatory variation of the serotonin transport gene. These various sources of epistasis possibly contribute to discrepant findings across studies, in addition to issues of population stratification, sex, and age.

The mechanisms through which these polymorphisms exert an effect are no doubt complex. The relationships between depression, cardiac disease, and adverse outcomes, although well documented, are not clearly understood and may not be unidirectional. Depression can precede and follow the onset of cardiac disease. One possible mechanism through which the L allele may exert an effect is through increased platelet activation, which has been shown to be elevated in patients with the LL genotype (29) and is elevated in depressed patients and which in turn is a risk factor for adverse cardiac events.

Surprisingly, neither candidate polymorphism in this current study is predictive of baseline depressive symptoms in our sample. One possible reason for this may be that patients with clinical diagnoses were excluded from enrollment, although despite this exclusion, we still find considerable incidence of depressive symptoms among our sample. It is also possible that anticipation of impending surgery could temporarily elevate CES-D scores, reflecting transitory cases of depressive symptoms which may resolve when surgery is completed. Genetic variability, as captured by these two polymorphisms, does not address the likelihood of developing depressive symptoms at 6 months or 1 year after surgery, beyond what is captured by knowing a patient's preoperative depressive symptoms.

Strengths of our study include the large sample of patients undergoing CABG surgery with pre- and postoperative depression assessments and analyses that accounted for potential confounding effects of gender and ethnicity. Study limitations include the fact that we did not document treatment for depression and therefore we do not know if treatment post CABG affected the observed incidence of cardiac events. There is a possibility that some patients who would otherwise be classified as having depressive symptoms at follow-up received treatment and thus were not identified as being depressed or that treatment of depression could have affected clinical outcomes. For example, heart failure patients receiving antidepressant medication actually had higher event rates compared with untreated patients (34). Second, the implications of excluding patients who were clinically depressed at baseline may have affected our analysis by eliminating patients with chronic depression. Again, this may have affected our ability to detect genetic associations with post-CABG symptoms. Third, we have examined the relationship between depressive symptoms and only two serotonin-related polymorphisms.

It is possible that the MAOA and 5HTTLPR polymorphisms are in linkage disequilibrium with other regulatory (causal) variants that were not evaluated in our study. Ideally, we would examine the cumulative genetic effects across multiple serotonin subsystems; however, this would require a much larger sample size than is available in our current study. Fourth, we have engaged in a number of exploratory and post hoc analyses, and our findings must be interpreted with caution in light of the multiple analyses strategies employed.

Despite substantial advances and improved outcomes post-CABG surgery, postoperative depression remains a serious concern. Because our results are somewhat novel, and not in complete agreement with the existing literature, it would be premature to propose using these polymorphisms for risk stratification; we must consider these results exploratory. However, the prognostic importance of depressive symptoms both before and after CABG has been demonstrated in several studies, and an improved ability to anticipate the occurrence of these depressive symptoms could prove valuable in reducing the adverse outcomes associated with CABG surgery, especially among depressed individuals.

Acknowledgments

Supported in part by Grants AG09663 (M.F.N.), HL54316 (MFN), AG17556 (D.A.S.), HL075273 (D.A.S.), and M01-RR-30 (Duke Clinical Research Centers Program) from the National Institutes of Health; and Grants 0256342U (J.P.M.), 9951185U (J.P.M.), 9970128N (M.F.N.), and 0120492U (M.V.P.) from the American Heart Association.

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Glossary

CABG	coronary artery bypass graft
CES-D	Center for Epidemiological Studies-Depression
PEGASUS	Perioperative Genetics and Safety Outcomes Study
MI	myocardial infarction
MAOA	monoamine oxidase A
VNTR	variable number of tandem repeats
L	long
L/L	long/long
S/S	short/short

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Figure 1. Incidence of new cardiac event, categorized by baseline depressive symptoms and 5HTTLRP genotype. Patients with depressive symptoms and the L allele experienced more frequent adverse events in the 2 years post surgery compared to patients with the SS genotype (as indicated by asterisks).

Table 1
Characteristics of the Study Population

	Total Sample (n = 427)	Males (n = 299)	Females (n = 128)	p
Age (years)	61. ± 10.9	62.6 ± 11.0	64.4 ± 10.8	.02
White race (%)	87.5	90.6	80.7	<.001
Duration of CPB (min)	117.7 ± 48.5	117.5 ± 48.5	117.0 ± 48.4	.88
Cross-clamp time (min)	65.1 ± 33.8	64.6 ± 32.2	66.1 ± 37.2	.55
LVEF (%)	54.1 ± 11.6	53.6 ± 11.5	55.2 ± 11.6	.05
Bypass grafts (#)	2.7 ± 1.4	2.8 ± 1.3	2.4 ± 1.4	<.001
History of hypertension (%)	62.0	57.9	71.1	<.001
History of diabetes (%)	28.5	24.4	37.7	<.001
ASA class IV ^a (%)	61.55	61.79	61.06	.83
CCS Class IV angina (%)	57.7	59.5	56.8	.42
Previous MI (%)	45.0	48.6	37.0	.007
Preoperative CES-D score	12.9 (10.5)	11.1 (9.6)	17.2 (11.2)	<.001

CPB = cardiopulmonary bypass; LVEF = left ventricular ejection fraction; ASA = American Society of Anesthesiologists; CCS = Canadian Classification System; MI = myocardial infarction; CES-D = Center for Epidemiologic Studies-Depression.

Values are mean ± standard deviation or percentage; *p* values compare the males and females; categorical comparisons are made with exact χ^2 test; continuous variables are compared with a Wilcoxon rank sum test.

^aClassification of preoperative physical status according to system developed by American Society of Anesthesiologists (ASA).

Table 2
Prevalence of Depressive Symptoms in the Study Population

<i>n</i>	No Symptoms of Depression (CES-D = <16)		Mild Symptoms of Depression (CES-D = 16–26)		Moderate-to-Severe Symptoms of Depression (CES-D = >27)		
	Males (%)	Females (%)	Males (%)	Females (%)	Males (%)	Females (%)	
Baseline	427	72	43	21	40	7	17
6 months	420	84	67	13	20	4	13
1 yr	411	83	68	13	19	4	13

CES-D = Center for Epidemiologic Studies-Depression.

Table 3
Association of 5HTTLPR Genotypes and Depressive Symptoms

	6-Month Depressive Symptom			1-Year Depressive Symptoms		
	Wald χ^2	OR (95% CI)	p	Wald χ^2	OR (95% CI)	p
5HTTLPR - LL	0.15	1.09 (0.72–1.64)	.70	4.96	1.76 (1.07–2.88)	.02
Female	21.02	2.57 (1.72–3.86)	<.0001	8.97	2.12 (1.30–3.47)	.003
Caucasian race	8.29	0.58 (0.33–1.02)	.004	2.82	0.56 (0.29–1.10)	.09
Age	3.61	0.97 (0.96–0.99)	.06	1.92	0.98 (0.96–1.01)	.17

OR = odds ratio; CI = Confidence Interval.

Table 4
Incidence of New Cardiac Event Within 2 Years of CABG Surgery, Classified by Genotype and Baseline Depressive Symptoms

	Percent of Patients With Adverse Cardiac Event	
	No Depressive Symptoms at Baseline (<i>n</i> = 270)	Depressive Symptoms at Baseline (<i>n</i> = 157)
5HTTLPR genotype ^a		
L/L	7.94	17.33
S/L	8.05	21.78
S/S	8.33	13.51
MAOA genotype ^b		
Males		
3	9.32	17.07
4	7.53	18.18
Females		
3/3	0	23.53
3/4	10.71	21.95
4/4	7.69	17.5

CABG = coronary artery bypass graft; MAOA = monoamine oxidase A.

^aSignificant interaction was found between the presence of the L allele and presence of depressive symptoms at baseline ($p < .05$).

^bSimilar (nonsignificant) results were found using the efficiency categorization of MAOA genotypes.