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Sex-Specific Association of Depression and a Haplotype in Leukotriene A4 Hydrolase Gene

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Abstract

Objective—To assess whether genetic variants involved in inflammation play a role in the sex difference in depression. Depression is, in part, genetically determined and inflammation has been implicated. Women are twice as likely to develop depression as men.

Methods—We examined the association, separately in men and women, between seven single nucleotide polymorphisms (SNPs) in the arachidonate 5-lipoxygenase-activating protein (ALOX5AP) gene and 12 SNPs in the leukotriene A4 hydrolase (LTA4H) gene and depression in 1368 white subjects (30.4% female) referred for cardiovascular evaluation. Depression was defined as a score of ≥ 10 in the Patient Health Questionnaire 9. Single marker analysis was assessed by the χ^2 test. Haplotype-specific associations were performed, using likelihood ratio tests. Empirical significance levels were determined by permutation tests.

Results—Depressed individuals, comprising 14.5% of the total, were more likely to be female, current smokers, have a history of diabetes and myocardial infarction. None of the SNPs in the ALOX5AP gene, either singly or in combination, was associated with depression. The 12 SNPs in the LTA4H gene were not individually associated with depression. However, a six-SNP haplotype in LTA4H gene, named HapE, showed a significant protective effect on depression in women, but not in men, after correcting for cardiovascular effects. The interaction between HapE and sex on depression was statistically significant.

Conclusion—This study provides the first evidence for a sex-specific association of a novel haplotype in the LTA4H gene on depression. Although replication is needed, our study suggests that genetic variations may underlie sex differences in depression.

Keywords

depression; sex difference; SNP haplotype; leukotriene; genetic association

INTRODUCTION

Depression is common and a major cause of morbidity and mortality (1,2). Women are about twice as likely to experience depression compared with men (3). In addition, in women, depression tends to be of earlier onset, longer duration, and greater severity compared with men (4). The presentation and course of depression tend also to be different in women and men (2,5). Although several hypotheses including genetic (6), biological (5), and social/psychosocial factors (7) have been proposed to explain the differential risk of major depression in males and females, none has been proven.

Major depression is, in part, genetically determined (2,6,8). Monozygotic twins have a higher concordance rate than dizygotic twins for major depression (2,9). The heritability of major depression is significantly higher in women than in men (10,11). In addition, the genetic correlation of the liability to major depression in men and women is substantially less than one, suggesting that a significant proportion of the genetic factors for depression have differing effects on the two sexes (10,11). Evidence for sex-specific genomic regions has also been found for depression and other psychiatric disorders (12,13). However, the genetic basis underlying the sex difference in major depression remains unclear.

Inflammation plays a key role in the pathophysiology of depression (14). Depressed individuals exhibit higher levels of inflammatory biomarkers, such as cytokines, compared with nondepressed individuals (14,15). Administration of cytokine antagonists can effectively reverse depressive symptoms, and antidepressants can inhibit the production and/or release of proinflammatory cytokines (14–16). Leukotrienes are the most potent inflammatory mediators (17–19) and are essential for normal brain function (20,21). To the extent that inflammatory processes are causal in depression, it follows that genetic variants in key enzymes involved in the leukotriene pathway may influence the susceptibility to depression. Moreover, there is evidence for sex differences in the metabolic pathway of leukotriene biosynthesis. For instance, Pergola et al. demonstrated that more leukotriene B₄ and other 5-lipoxygenase products were produced in stimulated blood and neutrophils (the primary source of 5-lipoxygenase products in the blood) from women compared with those from men (22). The goal of this study is to examine whether genetic variants in the genes encoding the two key leukotriene enzymes, ALOX5AP and LTA4H, are implicated in the sex disparity of depression in a well-characterized patient cohort.

MATERIALS AND METHODS

Subjects

Subjects were participants in the Emory Cardiac Genebank Study, an ongoing prospective registry of patients undergoing cardiac catheterization at Emory University clinical sites starting in 2004. The purpose of this study is to investigate the effects of genetic factors and novel cardiovascular risk markers on angiographically documented coronary artery disease (CAD). Patients were approached for the study when they were in the catheterization laboratory. Each patient was interviewed to collect information on demographic characteristics, personal and familial medical history, behavioral (lifestyle) factors, and depressive symptoms. Fasting blood samples were collected at the time of cardiac catheterization for genetic analysis and biochemical assays. All subjects provided their written informed consent. The Emory Cardiac Genebank Study has received Institutional Review Board approval by Emory University.

Assessment of CAD

A medical history of the patient and the patient's family and a physical examination were obtained from all participants. Cigarette smoking was classified into current smoker (any

number of cigarettes) vs. never smoked or past smoker. History of diabetes, hypertension, and myocardial infarction (MI) was physician diagnosed.

The coronary angiograms for patients were reviewed and coded by two investigators blinded to the patients' clinical condition and laboratory information. Reliability for the readings was assessed by correlating the results of the same angiogram coded by the two investigators. The interobserver correlation was 0.86. CAD severity was scored by counting the number of vessels with $\geq 50\%$ stenosis, based on lesions within the major epicardial vessels (left anterior descending, left circumflex, and right coronary artery) or their major branches.

Measure of Depression

To assess depressive symptoms, each participant was asked to complete the Patient Health Questionnaire 9 (PHQ9), a brief, nine-item, self-administered instrument that enables screening for depression and assessment of depression severity. The nine items of the PHQ9 come directly from the nine symptoms of major depression used to diagnose major depression according to the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) (23,24). For each of the nine depressive symptoms, patients indicated whether, during the previous 2 weeks, the symptom had bothered them "not at all," "several days," "more than half the days," or "nearly every day," yielding a score of 0 to 3. The PHQ9 score thus ranges from 0 to 27, with a higher score indicating severe depression. Validation studies have demonstrated that the PHQ9 has excellent reliability, validity, sensitivity, and specificity (23,24).

In this study, we defined depression as having a PHQ9 score of ≥ 10 (24). This cutoff has a sensitivity of 88% and a specificity of 88% for identifying correctly patients with major depression and those with no depressive disorder, respectively (24). Only individuals who completed all the nine items in the PHQ9 were included in this analysis.

Genotyping

A total of 19 single nucleotide polymorphisms (SNPs) (7 SNPs in the ALOX5AP gene including rs17222814, rs17216473, rs10507391, rs4769874, rs9551963, rs9315050, and rs17222842 on chromosome 13, and 12 SNPs in the LTA4H gene including SG12S16, rs2660880, rs6538697, rs1978331, rs17677715, rs2247570, rs2660898, rs2660899, rs2540482, rs2660845, rs7966098, and rs2540475 on chromosome 12) were genotyped in 1368 individuals (198 depressed patients and 1170 controls). SG12S16 is an SNP mapped by deCODE Genetics (25). There is no public name available for this marker.

All SNPs were identified by sequencing deoxyribonucleic acid (DNA) across the gene regions in 93 patients with MI and 93 controls (26,27). These SNPs were genotyped by deCODE Genetics of Iceland, in partnership with the Emory Cardiac Genebank Study. The call rates of typed SNPs were $>99\%$ and concordance rates with controls or blinded data were $>99.5\%$. These SNPs were selected to capture all haplotypes with a frequency of $>2\%$ across the gene regions. Details for the identification and selection of these SNPs have been previously described (26,27).

Statistical Analysis

Differences in baseline characteristics between participants with and without depression were compared, using analysis of variance for continuous variables and χ^2 tests for dichotomous variables. Differences were considered significant at an α level of 0.05.

Hardy-Weinberg equilibrium and linkage disequilibrium estimates were calculated, using Haploview 3.0 (28). The distribution of frequencies at the allele and haplotype level between cases and controls was compared, using the program WHAP (29). The single marker analysis uses a χ^2 test. The haplotype analysis uses a regression-based association test through a likelihood ratio test, which is a χ^2 test with $n - 1$ df to determine the associated p value, where n represents the number of haplotypes observed for the data set. This test was also used for testing the effect of an individual haplotype on the risk of depression, i.e., haplotype-specific association tests ($df = 1$). Due to the large number of haplotype combinations, we only analyzed two-SNP, three-SNP, and up to six-SNP haplotypes from adjacent SNPs of the seven markers in ALOX5AP and the 12 markers in LTA4H, separately, using the “sliding-window” technique implemented in WHAP. Haplotypes with frequencies of $<1\%$ were ignored. Empirical significance levels for both single marker and haplotype analyses were determined by 10,000 permutation testing (i.e., “case” and “control” labels are randomly reassigned to the actual data), and were corrected for the number of analyses performed, taking into account linkage disequilibrium between markers. The relationship between each haplotype and depression was further determined, using logistic regression, by defining subjects carrying at least one copy of a specific haplotype as haplotype carriers, and those not carrying the specific haplotype as noncarriers. The adjusted odds ratio (OR) and 95% Confidence Intervals (CIs) were calculated after adjusting for CAD and all baseline differences between the depressed and nondepressed groups, including age, smoking, and history of diabetes and MI. All genetic association analyses were performed separately in men and women because of the potential difference in genetic substrate for depression in the two sexes (6,10). The interaction between HapE and sex was tested in a separate logistic regression model with depression as the dependent variable, and HapE carrier status (carrier versus noncarrier), sex (male versus female), HapE $\times$ sex and coronary risk factors including CAD, age, smoking, and history of diabetes and MI as independent variables. To avoid false-positive results due to population stratification, this analysis only included white participants. Moreover, we tested the effect of population stratification, using the STRUCTURE program (30).

To determine whether CAD severity mediated the association between depression and genetic variants, we performed ordinal logistic regression in which CAD severity, as an ordinal variable with five levels, was the dependent variable, and depression or genotypes were the independent variables. To examine whether a recent acute clinical episode (e.g., MI or unstable angina), which may have prompted the catheterization, confounded the association between depression and genotypes, we tested the association between a recent clinical event and depression, as well as the association between a recent clinical event and genotype, by χ^2 tests. All analyses were done separately in men and women and were corrected for known coronary risk factors.

RESULTS

In total, 1368 individuals ($n = 416$ women and 952 men) were included in the analysis. The prevalence of depression was 18.8% in women and 12.6% in men. Table 1 presents the characteristics of the study population according to the status of depression assessed by the PHQ9. Females were more likely to be depressed than males. Among the depressed group, frequencies of Type 2 diabetes, and MI were significantly higher than in the nondepressed group. In addition, individuals with depression were more likely to be smokers compared with nondepressed individuals (all $p < .005$).

We did not find any evidence for population stratification in the study sample. All studied SNPs were in Hardy-Weinberg equilibrium. None of the markers in the ALOX5AP, either alone or in combination, showed significant association with depression. The 12 SNPs in

LTA4H gene were not individually associated with depression. However, a six-SNP haplotype in the LTA4H gene, named HapE, showed a significant protective effect on depression in women but not in men.

Compared with individuals without HapE, subjects with HapE were less likely to report a history of diabetes, hypertension, and MI. The differences in clinical variables according to HapE carrier status is listed in Table 2, which shows that HapE carriers tended to have a lower frequency of CAD and depression compared with HapE noncarriers, indicating a protective effect of HapE on these factors. There was no association between depression and CAD severity ($p = .19$).

HapE contains six SNPs, including SG12S16(C), rs1978331(G), rs17677715(T), rs2660899(G), rs2540482(T), and rs2660845(A). It has four overlapping SNPs with the risk HapK defined by Helgadottir et al. (26), but the susceptibility alleles in three of them have flipped bases. This may provide an intuitive explanation for the opposite effects of the two haplotypes on risk of atherogenesis. Moreover, HapE defined in this study is distinct from HapK in that they are mutually exclusive, i.e., people who carry HapE are unlikely to have HapK and vice versa. Table 3 lists the difference between HapE and HapK.

HapE was more prevalent in women than in men (17.2% versus 13.9%) but the difference was statistically nonsignificant ($p = .16$). The prevalence of HapE was 6.4% among depressed women and 19.7% among nondepressed women. Corresponding frequencies in men were 13.7% and 13.9%. HapE carrier status was significantly associated with depression in women (OR = 0.28, 95% CI = 0.11–0.72, $p = .008$), but not in men (OR = 0.98, 95% CI = 0.56–1.72, $p = .94$). The observed association in women persisted materially unchanged after accounting for the effect of CAD and baseline differences (OR = 0.27, 95% CI = 0.09–0.78, $p = .016$), suggesting that the protective effect of this haplotype on depression in women may not depend on CAD and traditional risk factors (Figure 1). The interaction between HapE and sex was statistically significant ($p = .026$), and correction for CAD and baseline differences has no influence on the haplotype $\times$ sex interaction ($p = .027$). Figure 2 illustrates the interaction between HapE and sex on risk of depression. HapE carriers were three times less likely to be depressed compared with HapE noncarriers ($p = .005$) in women, whereas the HapE carrier status did not predict depression in men ($p = .94$). The observed association between HapE and depression persisted when a continuous measure of depression score was used in the analysis (to achieve normality, depression score was logarithmically transformed).

CAD severity was associated with depression in women (OR = 1.78, 95% CI = 1.09–2.91), but not men (OR = 1.13, 95% CI = 0.77–1.65). In addition, CAD severity was associated with HapE in women (OR = 0.58, 95% CI = 0.35–0.96), but not men (OR = 0.78, 95% CI = 0.54–1.12). Mediation analyses (31,32) indicated that HapE partially mediated the observed association between CAD severity and depression in women ($p = .13$ by Sobel test), and about 7.1% of the association between depression and CAD severity was explained by HapE.

About 10% of the study participants were referred to angiography as a result of a recent clinical event (MI or unstable angina). However, a recent clinical event was not associated with depression in women: the prevalence of a clinical event was 17.4% in depressed and 12.5% in nondepressed women ($p = .41$). Furthermore, a recent clinical event was not associated with HapE in women: the prevalence of a recent clinical event was 7.9% in women with HapE and 17.8% in women without HapE ($p = .13$). The association between HapE and depression in women remained significant after excluding subjects with a concurrent clinical episode (OR = 0.24, 95% CI = 0.07–0.82).

DISCUSSION

We found a significant association between a novel haplotype in the LTA4H gene and depression in women, but not men. Substantial evidence suggests that genes may play a role in the sex difference noted in depression, although mixed results exist (33). For example, Kendler and Gardner (10) found that the heritability of major depression was 42% in women and 29% in men in Swedish twins. The corresponding heritability was 40% and 31% in a Virginia twin sample (6). Several other twin studies have also found higher heritability of major depression in women than in men (34–36).

The higher heritability for major depression in women than in men implies that genes may play a greater role in depression in women than in men. Moreover, twin studies demonstrated that the genetic correlation in liability to depression between men and women was substantially less than one (6,10), suggesting that the genes influencing susceptibility to major depression in the two sexes may not be entirely the same, or that common genetic pathways in men and women may operate differently in the two sexes due to differences in biological and/or psychosocial exposures between men and women (5,37). For example, a gene might alter the susceptibility to depression in women in response to the variable hormonal environment of the menstrual cycle and pregnancy (38,39), whereas such genes would not affect susceptibility to depression in men. It is also possible, however, that men and women have a different genetic architecture for depression (34,40). In this case, men and women will have distinct genetic loci and genetic pathways, and a substantial proportion of genes will be sex-specific in their effects on the risk of depression (6,10). This hypothesis is supported by several genome-wide scans for major depression, all of which have found evidence of sex-specific genomic regions in men or women (12,13,41). For example, in a genome-wide linkage analysis, Abkevich et al. (13) found strong evidence for the existence of a major depression-predisposition gene on chromosome 12q22-q23.2 in males, but not in females. Another genome-wide linkage for depression and anxiety demonstrated that the female-specific linkage peaks on chromosomes 1, 7, and 12 could not be replicated in males, and the male-specific linkage regions on chromosomes 6 and 17 could not be replicated in females (12). Sex-specific genomic regions were also reported for other psychiatric disorders, such as neuroticism (42), autism (43), and suicide (44,45), of which neuroticism has a substantial genetic overlap with depression (46,47).

Depression is an independent risk factor for and often comorbid with cardiovascular disease (48,49). Common genetic vulnerability has been proposed as an explanation for the comorbidity between these two disorders (3,50). Our finding of an association between HapE and depression, taken together with the reported associations between other leukotriene haplotypes (HapA, B, and K) and cardiovascular diseases (26,27,51,52), suggests that the leukotriene metabolic pathway is a likely candidate in the search for a common genetic mechanism linking depression and cardiovascular disease. This result may explain why both depression and cardiovascular disease have been linked to an increased inflammatory response. In addition, sex has been shown to be an important modifier in the link between depression and cardiovascular disease (3). For instance, depression is more prevalent in women post acute MI compared with men (3), and depressive symptoms are more severe and persist longer in women than in men (3). Our finding may also help explain the observed sex difference in the connection between depression and cardiovascular disease.

Our study has limitations. First, the samples used in this analysis were from a single-center patient population referred for cardiac catheterization. Given the comorbidity of cardiovascular disease and depression, our sample may differ from a sample selected randomly from the general population. Therefore, our results may not be generalizable to a

noncardiac population. Nonetheless, the observed genetic association in women and the significant interaction between HapE and sex on depression were independent of cardiovascular effects, which were corrected for in all statistical analyses. Second, as in all case-control studies, our finding may represent a false-positive due to population substructure. However, we limited our analyses to white participants only, and did not find evidence for population stratification in our study sample. Third, given that all participants were referred for angiography, it is possible that the observed association between LTA4H polymorphism and depression in women may be confounded by a concurrent clinical episode, such as MI or unstable angina. However, this is unlikely the case for this study because a recent clinical episode (MI or unstable angina) was not associated with either depression or HapE in women. The association between HapE and depression in women persisted after excluding subjects with a concurrent clinical episode. Therefore, the observed correlation between HapE and depression in women should reflect a direct effect of LTA4H variations on depression, rather than an indirect effect by the association with a depressive response to heart disease. It is also unlikely that the observed association between HapE and depression in women was mediated by CAD severity because we have controlled for CAD throughout the statistical analysis. The fact that HapE is associated with both depression and CAD severity in women is in support of a pleiotropic role of this genetic polymorphism in CAD and depression among women. Finally, because the average age of our study population is relatively old (mean age = 62.7 years), it is unclear if our findings are extendable to younger adults.

In summary, the present study provides the first evidence for a novel leukotriene haplotype in the interplay between sex and depression. Although the underlying mechanism for HapE in the sex differences of depression remains uncertain at the present time, this finding opens a new window into the pathophysiology underlying the sex disparity in depression, and provides impetus for new research directions in the study of the links among sex, depression, and cardiovascular disease. Furthermore, these data provide support for future sex-specific approaches in preventive efforts to better screen for and treat depression in the community.

Glossary

SNPs	single nucleotide polymorphisms
ALOX5AP	arachidonate 5-lipoxygenase-activating protein
LTA4H	leukotriene A4 hydrolase
CAD	coronary artery disease
PHQ9	Patient Health Questionnaire 9.

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Figure 1.

Association between HapE and depression. *Adjusted for age, smoking, coronary artery disease, history of diabetes, and history of myocardial infarction. OR = odds ratio; HapE = six-SNP haplotype in LTA4H gene.

Figure 2. Prevalence of depression by sex and HapE carrier status. HapE = six-SNP haplotype in LTA4H gene.

TABLE 1

Characteristics of the Study Participants According to Depression Status

Variables	PHQ-9 ≥ 10 (<i>n</i> = 198)	PHQ-9 <10 (<i>n</i> = 1170)	<i>P</i>
Demographic			
Age (years)	61.2 $\pm$ 12.3	64.2 $\pm$ 10.9	.002
Female (%)	39.4	28.9	.003
White (%)	83.3	82.5	.86
Current smoking (%)	22.3	12.2	< .001
Body mass index (kg/m ²)	29.9 $\pm$ 5.9	29.9 $\pm$ 7.3	.99
Self-reported medical history			
Type 2 diabetes (%)	38.5	26.4	< .002
Hypertension (%)	68.1	63.2	.20
Myocardial infarction (%)	47.7	37.3	.005
Other characteristics			
CAD severity score (by angiograms)	2.4 $\pm$ 1.4	2.3 $\pm$ 1.5	.53

SD = standard deviation; PHQ = Patient Health Questionnaire; CAD = coronary artery disease.

Data are presented as mean $\pm$ SD unless otherwise noted.

TABLE 2

Characteristics of the Study Participants According to HapE Carrier Status

Variables	HapE Carriers (<i>n</i> = 187)	HapE Noncarriers (<i>n</i> = 1181)	<i>p</i>
Demographic			
Age (years)	64.5 ± 10.5	63.9 ± 11.2	.51
Female (%)	34.9	30.6	.26
Current smoking (%)	12.6	14.2	.57
Body mass index (kg/m ²)	29.6 ± 5.4	30.1 ± 7.6	.55
Self-reported medical history			
Type 2 diabetes (%)	23.2	27.1	.53
Hypertension (%)	58.7	64.3	.14
Myocardial infarction (%)	24.1	41.8	< .001
CAD (yes/no, %)	45.2	52.2	.28
Other characteristics			
CAD severity score (by angiograms)	2.1 ± 1.5	2.4 ± 1.4	.008
Depression (%)	11.8	15.8	.19

Data are presented as mean ± SD unless otherwise noted.

TABLE 3

Difference between HapE and HapK

SNPs in HapE (susceptibility allele)	SNPs in HapK (susceptibility allele)
SG12S16 (C)	—
rs1978331 (G)	rs1978331 (A)
rs17677715 (T)	rs17677715 (T)
rs2660899 (G)	—
rs2540482 (T)	rs2540482 (C)
rs2660845 (A)	rs2660845 (G)
—	rs2540475 (G)

HapE = six-SNP haplotype in LTA4H gene; HapK = five-SNP haplotype in LTA4H gene; SNPs = single nucleotide polymorphisms.