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Association of serotonin-1A and 2A receptor promoter polymorphisms with depressive symptoms and functional recovery in elderly persons after hip fracture

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Abstract

Background—Depression is common after hip fracture and is associated with poorer functional recovery. Polymorphisms of the serotonin 1a (5HTR1A) and 2a receptors (5HTR2A) are associated with depression; therefore, we examined their association with depressive symptoms and functional recovery after hip fracture.

Methods—145 elderly women were followed for 12 months after hip fracture. Depressive symptoms were measured with the 15-item Geriatric Depression Scale (GDS). Functional status was measured by Lower Extremity Physical and Instrumental Activity of Daily Living scales (LPADLs and IADLs). Time-adjusted general linear regression models compared mean GDS between those with and without risk alleles for 5HTR1A and 5HTR2A.

Results—Women with 1–2 copies of the 5HTR1A (−1019) G allele had higher GDS scores (Adjusted Mean Difference=0.59; 95% CI, 0.12–1.06), and poorer IADL scores (Adjusted Mean Difference=0.24; 95%CI −0.002–0.49), compared to those without this allele, controlling for potential confounders and 5HTR2A. Depressive symptoms partly accounted for poorer IADL recovery. Women with 1–2 copies of the 5HTR2A (−1438) C allele did not have significantly higher GDS scores (Adjusted Mean Difference=0.34; 95%CI, −0.20–0.87) and had better IADL scores (Adjusted Mean Difference=−0.40; 95%CI −0.74--0.06) than those with A/A genotype.

Limitations—The findings are limited by small sample size and the use of a screening scale to measure depression.

Conclusions—The 5HTR1A (−1019) G allele is associated with increased depressive symptoms after hip fracture, which in turn accounts for poorer functional recovery. These results suggest a role for serotonergic genetic variation in elderly persons' resilience and recovery from medical events.

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Introduction

Disabling medical events are common and severe life events for elderly persons (Hardy et al, 2004). For example, studies have found high rates of depressive symptoms after a hip fracture (Billig et al, 1986; Magaziner et al, 2000; Mossey et al, 1990; Lenze et al, 2007). Depressive symptoms in the context of a hip fracture have adverse effects on functional recovery (Magaziner et al, 2000; Mossey et al, 1990; Holmes & House, 2000; Lenze et al, 2004). However, many hip fracture patients do not suffer depression; the sources of this variability are largely unknown. The serotonin system modulates behavioral response to stress, including depressive symptoms (Duman et al, 2000), but it is unclear whether serotonergic modulation of stress response is similar in elderly (Hickie et al, 2007; Steffens et al, 2007). A small study of elderly hip fracture patients and a large study of Korean elders both found an association of the serotonin transporter promoter with depression after stressful life events (Lenze et al, 2005; Kim et al, 2007).

Other serotonergic genes are also candidates for modifying risk for depressive symptoms in the context of a stressful event. 5HTR1A is an autoinhibitor of serotonin release; the (−1019) C/G polymorphism in its promoter has been associated with MDD in some (Lemonde et al, 2003) but not all (Arias et al, 2002) studies, with higher depression rates associated with the G allele (Lemonde et al, 2003). Also, 5HTR2A is a mediator of the downstream effects of serotonin; the (−1438) A/G polymorphism in its promoter is associated with MDD, with one study reporting higher rates with the G allele (Choi et al, 2004); conversely, a study in elderly persons found that the A/A genotype was associated with depressed mood, in males only (Jansson et al, 2003).

These polymorphisms in these genes may predict depressive symptoms in the context of hip fracture, which in turn may predict functional recovery. Therefore, the present study examined these two genetic loci in a prospective study of hip fracture. We hypothesized that the risk alleles would predict greater depressive symptoms after the fracture. Additionally, as depression is predictive of poorer functional recovery, we hypothesized that the risk alleles would predict poorer ADL and IADL function over the one year following hip fracture, and that the poorer recovery would be mediated, or accounted for, by greater depressive symptoms. Confirmation of these hypotheses would suggest that genetic variability in the serotonergic system affects elderly persons' psychological and functional outcome after a medical event.

Methods

Sample

Data for this analysis were from the study "Bone/muscle changes following hip fracture in older white women", a prospective study of the effect of an exercise intervention on parameters of hip fracture recovery. The study recruited females aged 65+ admitted to three Baltimore-area hospitals from 1998–2004 who suffered a hip fracture within 72 hours of their hospitalization, had surgical repair of their hip, and had been living in the community prior to the fracture. To select subjects who would be likely to perform the study assessments and participate in this year-long study, exclusions included presence of cardiovascular disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, seizure disorder, respiratory conditions, diseases of the bone (such as Paget's disease or osteomalacia), metastatic cancer, cirrhosis, end-stage renal disease, dementia, alcohol abuse, narcotic or benzodiazepine use, or recent gastrointestinal bleeding. Subjects had to be ambulatory prior to the fracture and have a Mini-Mental Status Exam score greater than 20 to participate. The study received University of Maryland IRB approval and all subjects provided written informed consent.

Measures

Demographics were determined by self-report. Several measures assessed clinical status within 15 days post-fracture and then two, six, and 12 months post-fracture: the 15-item version of the Geriatric Depression Scale (GDS), a valid method of screening for, and measuring severity of, depressive symptoms in medically ill elderly persons (Almeida et al, 1999); a modified Charlson score, an index of comorbid conditions (Charlson et al, 1987); an 11-item Lower extremity Physical Activities of Daily Living (LPADL) scale (items: walking across a room; walking one block; climbing stairs; getting into a car; getting into and out of bed; rising from a chair; putting on pants; putting on socks and shoes; bathtub transfer; taking a bath/shower; and toilet transfer); and a seven-item Instrumental Activities of Daily Living (IADL) scale (items: using telephone; getting to places out of walking distance; shopping for groceries; preparing meals; housecleaning; handling money; taking medications). For LPADL and IADL scores, persons received one point for each activity they were unable to perform without assistance; thus, higher scores indicated greater disability; subjects' pre-fracture function was also assessed; GDS, LPADL, and IADL measures were assessed via subject self-report.

Genotyping

Genetic samples were provided from blood draws which were obtained from all subjects within 15 days of hip fracture, which were frozen and later shipped for genetic analysis. High molecular weight DNA was isolated from frozen cell pellets by standard procedures (Miller et al, 1998), and the 5HTR1A (−1019) (rs 6925) and 5HTR2AA (−1438) (rs 6311) were genotyped by the fluorescence polarization method of Chen et al (1999).

Statistical Analysis

Pre- and post-fracture characteristics were examined for different genotypes of 5HTR1A and 5HTR2A, and for those with conclusive genotyping results vs. those with inconclusive results, using two-sample t-tests and Fisher's exact tests. The purpose of the study was to examine the relationships of genetic variation in 5HTR1A and 2A with depressive symptoms and disability post-fracture. Therefore, general linear regression models, a special case of generalized estimating equations (GEE) (Liang & Zeger, 1986), fit using xtgee in Stata, were estimated to compare mean GDS score between those with and without the risk allele for 5HTR1A and 5HTR2A controlling for time since hip fracture. For each model (5HTR1A and 5HTR2A separately and combined additively) two models were fit: one adjusted for time since hip fracture and the other adjusted for time since fracture and baseline/pre-fracture covariates (baseline age [truncated at 90], levels of education, Charlson comorbidity score, pre-fracture LPADLs, and pre-fracture IADLs). We did not control for ethnicity, as only six participants were African American (rest Caucasian). We controlled for time by including indicator variables for follow-up visits at 2, 6, and 12 months. Thus our GEE base models (genotype and time only) are robust analysis of variance models with no interaction terms; our rationale was to parsimoniously assess the overall relationship between genotype and our outcomes while still accounting for changes in the outcomes over time. For all models, 95% confidence intervals were calculated for differences in adjusted mean GDS scores, ADLs, and IADLs; robust standard errors were used to account for intra-person correlation over time. Exact tests assessed for departures of genotype frequencies from Hardy-Weinberg equilibrium (Emigh, 1980).

Results

Baseline characteristics of the sample

Among the 180 participants enrolled, two were excluded for dementia, three did not provide DNA for genotyping and 30 provided DNA that produced inconclusive results; thus, 145

subjects comprised the sample for this analysis. Pre-and post-fracture characteristics are presented in Table 1. Genotype groups did not differ with respect to these characteristics. Genotypes did not deviate from Hardy-Weinberg equilibrium (5HTR1A p=0.40, 5HTR2A p=0.86). Those whose genotypes could not be determined were older (mean [SD]=83.3 [7.1], p=0.07]), had more pre-fracture LPADL disability (2.36 [2.55], p=0.24), and had more pre-fracture IADL disability (1.70 [1.59], p=0.04). Among the 145 study participants with determined genotypes, ten had no risk alleles, 85 had risk alleles at both genes, 15 had a risk allele at 5HTR1A only, 34 had a risk allele at 5HTR2A only, and one had a risk allele at 5HTR1A but inconclusive results at 5HTR2A. All 145 participants had a GDS score at baseline; GDS scores were obtained at baseline, 2, 6, and 12 months post-fracture for 144, 127, 133, and 130 subjects, respectively. The mean (SD) GDS at 2 weeks and 2, 6, and 12 months post-fracture were 2.5 (2.7), 3.4 (2.7), 3.0 (2.6), and 3.3 (2.9), respectively.

Genetic associations with depressive symptoms

The estimated mean differences in GDS by genotypes are found in Table 2. Controlling for time since hip fracture, age, comorbid conditions, pre-fracture LPADLs and IADLs, and 5HTR2A, those with at least one copy of the 5HTR1A risk allele had average GDS scores 0.63 (95% CI 0.16–1.10) higher than those without the risk allele (p=0.009). In the same model, those with at least one copy of the 5HTR2A risk allele had average GDS scores 0.37 (95% CI −0.17–0.91) higher than those without the risk allele, but this difference was not significant (p=0.18).

Genetic associations with disability

Table 2 displays mean differences in IADL dependencies across genotypes. Those with the 5HTR1A risk allele had 0.24 (95% CI −0.002–0.49) more IADL dependencies than those without the risk allele, controlling for time since hip fracture, baseline and pre-fracture covariates, and 5HTR2A genotype (p=0.05). In contrast, those with the 5HTR2A risk allele had 0.40 fewer IADL dependencies (95% CI 0.06–0.75, p=0.02). Differences in LPADLs between genotypes for both 5HTR1A and −2A were not statistically significant (data not shown), though the associations were in the same direction as for IADLs.

Depressive symptoms as a mediator of genetic association with IADL function

Depression was explored as a potential mediator between genotype and IADLs by including time-lagged GDS in the covariate-adjusted models described above (e.g., IADLs at 12 months regressed on GDS at 6 months, controlling for covariates and combined 5HTR1A and 5HTR2A). The effect of the 5HTR1A risk allele on IADL dependence was reduced and was non-significant (mean difference 0.14 [95% confidence interval −0.12–0.39, p=0.30]), after controlling for lagged GDS, supporting the hypothesis of depressive symptoms as a mediator of the 5HTR1A polymorphism effect on IADL function. In contrast, the decreased IADL dependence associated with the 5HTR2A risk allele was not attenuated (mean difference −0.47 [95% confidence interval −0.81 – −0.12, p<0.01]) after including lagged GDS in the model, suggesting that the association of 5HTR2A with reduced IADL disability is unrelated to depressive symptoms.

Sensitivity analysis with missing genotypes

The comparison between those with missing and observed genotypes suggested potential selection bias. The logistic regression for estimating the weights included education, age, pre-fracture ADLs, pre-fracture IADLs, two-week GDS, and comorbidities (Charlson score). The GEE results were robust to assumptions about missingness: most estimates using WEE increased in magnitude compared to the GEE estimates, and no significant associations using GEE became insignificant after using WEE (not shown).

Discussion

This study found that the 5HTR1A promoter polymorphism is associated with depressive symptoms, and functional recovery, in elderly persons after a hip fracture. The G allele of the 5HTR1A (−1019) polymorphism was associated with increased depressive symptoms and poorer recovery in IADLs for 12 months after the fracture. The poorer IADL recovery was partly explained by depression scores, suggesting that depressive symptoms partially mediated poorer IADL recovery. Such research is critical because little is known about the biological constructs underlying the role of late-life depression in recovery after medical events; these findings support the role of serotonergic transmission underlying this phenomenon.

In contrast, results were not consistent with this hypothesis for the 5HTR2A (−1438) polymorphism. These results may have been due to inadequate power in the sample. Contrary to our hypothesis, this group, which was hypothesized to be an at-risk group for depression after hip fracture, had better functional recovery in IADLs for the 12 months after hip fracture. It is possible that this polymorphism demonstrates adaptive trade-offs, with more emotional distress yet better functional recovery; or that the polymorphism is in linkage disequilibrium with another polymorphism responsible for this variation in functional recovery. However, replication of these results is needed. The negative results for both genes with LPADL scores may be consistent with the fact that studies examining late-life depression and functional recovery have more often found effects on IADLs than physical ADLs (Lenze et al, 2001).

The findings have important implications in several areas. First, few studies have examined serotonergic genetic variation and risk for depressive symptoms in elderly persons. The largest, a study of Danish twins, found linkage no association between 5HTR1A (−1019) and depressed mood; an association of 5HTR2A (−1438) was found, but in the opposite direction as hypothesized here (i.e., A/A homozygotes had higher depressed mood scores). The authors noted that serotonergic genetic variation may not be associated with depressed mood per se but with depression in the context of stressful life event (Christiansen et al, 2007); therefore our results do not contradict these prior results but taken together may explain the context of the effect of 5HTR1A variation on late-life depression. Such a gene-stress interaction approach supports the concept of depressive symptoms as the result of interplay between genetics and social-environmental stressors. Second, the findings suggest that genetic variability of serotonergic transmission has consequences not only for psychological response to the stress but also physical recovery from disability. Conceivably, pharmacologic manipulation at 5HT1a after a disabling medical event could reduce depressive symptoms and improve recovery. Thus, our finding recommends further examination of the serotonin system's role in functional recovery.

Our study has several limitations. First, it could not follow subjects from before the hip fracture (thus, we do not have a baseline depression score) and did not have depression diagnostic data or extensive functional data to track trajectories of recovery. Second, the sample size was small and utilized only a single screening measure for depression, which may have contributed to the negative results observed with the 5HTR2A polymorphism; further research should examine this and other attractive candidates in a larger study. Third, the study was of all females after a single type of medical event (hip fracture), and further research is needed to determine whether results would generalize to samples with different demographic and clinical characteristics. Fourth, antidepressant use data were not collected during the study; this may have been an important confounder. Fifth, we cannot eliminate the possibility that delirium was still present in some of the subjects and may have accounted for some of the relationship between depressive symptoms and functional recovery. Finally, it would be helpful to know whether the genetic relationship with depression is only seen at certain time points in the context of disabling medical event vs. throughout the recovery period, and future research examining

depression more comprehensively during the longitudinal recovery period should explore these alternatives. Serotonergic variation may affect risk for late-life depression differently than early-onset depression – because of vascular lesions (Steffens et al, 2007) or volumetric changes in mood circuitry (Taylor et al, 2005; Hickie et al, 2007).

Notwithstanding these limitations, study demonstrated an association of the 5HTR1A promoter polymorphism with depressive symptoms in elderly persons in the context of a medical event. Further, it demonstrated that genetic variation in the serotonin system predicted variability in functional recovery from a medical event. Additional research is needed to replicate this finding and to examine whether modulation of the serotonin system could reduce risk for late-life depression and improve elderly persons' resilience in terms of psychological and physical recovery following disabling medical events.

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Table 1

Baseline and pre-fracture characteristics of the sample

Variable	Overall N=145	Risk allele 5HTR1A N=101[1]	No risk allele 5HTR1A N=44	P-value[4]	Risk allele 5HTR2A N=119[2]	No risk allele 5HTR2A N=25	P-value[4]
Age, years[3] mean(SD)	81.2(6.7)	81.6(6.8)	80.6(6.6)	0.39	81.4(6.9)	80.8(5.9)	0.70
Race: number (%) African-American	6(4.1)	5(5.0)	1(2.3)	0.67	6(5.0)	0(0)	0.59
Education, years mean(SD)	12.2(3.7)	12.1(3.7)	12.7(3.6)	0.39	12.3(3.7)	12.1(3.8)	0.84
Medical comorbidity (Charlson Score) mean(SD)	1.07(1.30)	1.05(1.31)	1.11(1.28)	0.78	1.08(1.34)	1.08(1.15)	0.99
Pre-fracture lower-extremity ADLs mean(SD)	1.88(2.02)	1.89(1.94)	1.86(2.20)	0.94	1.92(2.04)	1.76(1.94)	0.72
Pre-fracture IADLs mean(SD)	1.13(1.34)	1.16(1.31)	1.05(1.43)	0.63	1.20(1.36)	0.84(1.28)	0.22
Baseline (2 weeks post-fracture) GDS mean(SD)	2.5(2.7)	2.7(2.7)	2.1(2.6)	0.19	2.6(2.7)	1.8(2.0)	0.12

[1] N=24 homozygotes, N=77 heterozygotes

[2] N=51 homozygotes, N=68 heterozygotes

[3] truncated at 90 years.

[4] p-values from t-tests for continuous variables and Fisher's exact test for categorical variables

Table 2

Mean increase in depression (GDS) scores and IADL disability post-fracture (with 95% confidence interval) in individuals with 5HTR1A or −2A risk alleles, compared to those without risk alleles in these genes.

		Genes included in models			
Model		**5HTR1A only**	**5HTR2A only**	**5HTR1A and 5HTR2A combined**	
				5HTR1A	**5HTR2A**
Time-adjusted model[a]	Depression (GDS scores)	0.66 (0.18, 1.14) P=0.007	0.43 (−0.13, 0.99) P=0.13	0.62 (0.13, 1.10) P=0.01	0.36 (−0.20, 0.93) P=0.21
	Disability (IADL scores)	0.35 (0.02, 0.67) P=0.04	−0.04 (−0.42, 0.34) P=0.82	0.35 (0.03, 0.68) P=0.03	−0.08 (−0.46, 0.31) P=0.70
Covariate and time-adjusted model[b]	Depression (GDS scores)	0.66 (0.18, 1.14) P=0.007	0.44 (−0.10, 0.98) P=0.11	0.61 (0.13, 1.09) P=0.01	0.37 (−0.16, 0.91) P=0.17
	Disability (IADL scores)	0.20 (−0.06, 0.47) P=0.13	−0.38 (−0.72, −0.03) P=0.03	0.22 (−0.04, 0.48) P=0.09	−0.40 (−0.74, −0.05) P=0.02

[a] Adjusted for time since hip fracture only.

[b] Adjusted for time since hip fracture, baseline age (truncated at 90 years) and comorbidities, and pre-fracture IADLs and lower-extremity ADLs.

Note: higher GDS scores include all timepoints post-fracture (2 weeks, and 2, 6, and 12 months), while higher IADL scores include 2, 6, and 12 months post-fracture.