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ORIGINAL RESEARCH

Translational genomic research: the role of genetic polymorphisms in MBSR program among breast cancer survivors (MBSR[BC])

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Abstract

Genetic variations of breast cancer survivors (BCS) may contribute to level of residual symptoms, such as depression, stress, fatigue, and cognitive impairment. The objective of this study was to investigate whether particular single-nucleotide polymorphisms (SNPs) moderated symptom improvement resulting from the Mindfulness-Based Stress Reduction for Breast Cancer (MBSR[BC]) program. An overarching goal of personalized medicine is to identify individuals as risk for disease and tailor interventions based on genetic profiles of patients with diseases including cancer. BCS were recruited from Moffitt Cancer Center and University of South Florida's Breast Health Program and were randomized to either the 6-week MBSR(BC) program ($n = 92$) or Usual Care ($n = 93$). Measures of symptoms, demographic, and clinical history data were attained at baseline, 6 weeks, and 12 weeks. A total of 10 SNPs from eight genes known to be related to these symptoms were studied using genomic DNA extracted from blood. Our results were examined for effect sizes, consistency, and statistical significance ($p < .05$). Three SNPs (rs4680 in COMT, rs6314 in HTR2A, and rs429358 in APOE) emerged as having the strongest (though relatively weak) and most consistent effects in moderating the impact of the MBSR program on symptom outcomes. Although effects were generally weak, with only one effect withstanding multiple comparisons correction for statistical significance, this translational behavioral research may help start the identification of genetic profiles that moderate the impact of MBSR(BC). The ultimate goal of this study is the development of personalized treatment programs tailored to the genetic profile of each patient.

Implications

Research: The impact of findings on researchers is a better understanding of the interplay between genetics and interventions aimed to improve quality of life among breast cancer survivors (BCS). The present research study identified a relationship between three single-nucleotide polymorphisms (SNPs; rs4680 in COMT, rs6314 in HTR2A, and rs429358 in APOE) and symptoms experienced by BCS to be investigated further in future research.

Practice: The impact of findings on practitioners is greater awareness of the impact of genetic profiles on symptom improvement after breast cancer treatment, which allows greater precision in health care planning. The three identified SNPs may help practitioners identify BCS at greater risk for symptom decline.

Policy: The impact of findings on policymakers is evidence of the importance of precision medicine in practice and policy, as the results of this study support the moderating effects of genetic profiles of BCS on Mindfulness-Based Stress Reduction intervention outcomes.

Keywords

Breast cancer, Mindfulness-Based Stress Reduction (MBSR), Genetic polymorphism

INTRODUCTION

Over 3.5 million breast cancer survivors (BCS) are currently living in the USA [1]. BCS outnumber all other groups of female cancer survivors [1], with up to a 90% survival rate 5 years after diagnosis [2]. Unfortunately, BCS often suffer late effects from cancer treatment, including anxiety, depression, sleep disturbances, fatigue, pain, cognitive dysfunction, and stress that can occur for months or even years after treatment ends [3–6]. BCS experience high symptom burden, with 70% of survivors reporting six or more adverse symptoms as related to treatment [7]. Often these debilitating symptoms can negatively affect the quality of life in BCS [8]. Considering the overwhelming majority of BCS are living long after completion of breast cancer treatment, it is imperative that effective therapies are directed toward their individual and specific needs.

Stress reduction techniques have been shown to decrease undesirable adverse effects in post-treatment BCS, improving quality of life [9]. In particular, Mindfulness-Based Stress Reduction for Breast Cancer (MBSR[BC]), a 6-week program adapted from Jon Kabat-Zinn's original 8-week program to

address the needs of women with breast cancer, was shown to reduce anxiety, depression, fatigue, and sleep disturbances [10–12].

With rapid recent advances in genomic sequencing technologies, extensive genomic research leads to identification of potential genomic variations associated with disease predisposition and response of treatments. Indeed, some previously identified gene variations have been translated into clinical settings in strategies of prevention and treatment decision [13–15]. For example, BRCA mutation analysis for predicting breast cancer risk has been integrated into oncology clinics [16]. Khoury and his colleagues reported that precision medicine for risk evaluation for cancer in the general population will be helpful. However, more research needs to determine whether implementation is beneficial or not [17]. A recent article reported that functional CYP2D6 single-nucleotide polymorphisms (SNPs) were significantly associated with adverse effect fatty liver following the tamoxifen therapy. Therefore, alternative treatment can be used for patients with CYP2D6 SNPs (rs28371725 and rs16947) [18].

For BCS experiencing psychological or physiological symptoms as result of treatment, greater understanding of the interplay between genetics and intervention outcomes can provide informed options for recovery. The general goal of precision medicine is to "ensure that patients get the right treatment at the right dose at the right time, with minimum ill consequences and maximum efficacy." [19] For our study, evaluating the relationship of the MBSR(BC) program among different genetic profiles is a step toward tailoring personalized health recommendations and care plans.

Currently, there are several genetic testing panels, using SNPs identified in genome-wide association studies, available for certain diseases [13–15]. However, only a few studies were performed on symptom outcomes and individual genomics [20–22]. Because of the complexity, such as outcome variables, sample size, and different distribution of genotypes in different racial populations, conducting translational behavioral investigation is challenging. Recently, we and others reported on symptoms in intervention studies with genetic influences [23–25]. The ongoing symptoms of BCS vary for each individual, and evidence has shown that there is a genetic influence on the frequency and intensity of the symptom experience [26, 27]. Based on our previous study, we hypothesize that candidate SNPs may be associated with a multitude of symptoms experienced by BCS and that the effects of our MBSR(BC) program may be moderated by these polymorphisms [23].

After an extensive literature search, we identified 10 SNPs and eight candidate genes related to symptoms experienced by BCS. Gene products considered included receptors, carriers, transporters, and metabolic enzymes in various pathways that may be related to various symptoms. SNPs in dopamine receptor 2 (*DRD2*) and solute carrier family 6 member 4 (*SLC6A4*) were reported to be associated with level of depression [28, 29] and pain [30]. Gene variations in apolipoprotein E (*APOE*), brain-derived neurotrophic factor (*BDNF*), serotonin receptor 2A *(5HT2A*), and methylenetetrahydrofolate reductase (*MTHFR*) were found to affect cognitive function [28, 29, 31–35]. SNPs in ankyrin repeat and kinase domain containing 1 (*ANKK1*) and catecholamine O-methyltransferase (*COMT*) were related to neuropsychiatric disorders and pain, respectively [36, 37].

The purpose of this study was to explore the relationship between SNPs in candidate genes and MBSR(BC)-related improvement in quality of life and psychological and physical symptoms among BCS within a large randomized controlled trial. Therefore, we investigated whether particular genetic variations moderated symptom improvement resulting from the MBSR(BC) program. An overarching goal of this personalized medicine project is to eventually tailor interventions based on genetic profiles of BCS.

METHODS

Participants

An initial subsample of BCS (N = 185) consented for genetic analysis within our NIH-supported randomized MBSR(BC) trial. BCS were recruited from Moffitt Cancer Center and the Carol and Frank Morsani Center for Advanced Healthcare, both located in Tampa, FL. The primary inclusion criteria were women age 21 or older diagnosed with stage 0, I, II, or III breast cancer who had undergone lumpectomy and/or mastectomy and were 2 weeks from the end of treatment with adjuvant radiation and/or chemotherapy to a maximum of 2 years from completion of treatment. Participant proficiency in English at the eighth-grade level was also required. Exclusion criteria included previous diagnosis of stage IV breast cancer and/or current diagnosis of a severe psychiatric disorder.

Procedures

Study design and randomization

This was a double-armed randomized controlled trial, with randomization determined by a blocked randomly generated number scheme. Random assignment was in a 1:1 ratio to one of the two conditions: (i) formal (in-class) 6-week MBSR(BC) program to commence within 1 week of the orientation session or (ii) Usual Care (UC) guidelines and waitlisted MBSR(BC) program offered within 6 months of enrollment into the study. Subject randomization

was stratified by type of surgery (lumpectomy vs. mastectomy), breast cancer treatment (chemotherapy with or without radiation vs. radiation alone), and stage of breast cancer (stage 0/I vs. II/III). Stratification was used in conjunction with the blocking mechanism to help insure balanced distributions of baseline factors between the two study groups.

Data collection

Clinic nurses identified eligible BCS that were subsequently approached by the study recruiter. BCS who expressed an interest in the program were invited to attend an orientation session for the MBSR(BC) program where baseline data was collected from patients who consented to participate in the study. This assessment included a blood sample, demographic and clinical history data, assessment of physical and psychological symptoms, and quality of life. Demographic and clinical history data were updated at the 6-week and 12-week follow-up. Similarly, assessment of physical and psychological symptoms, and quality of life were updated at 6 weeks and 12 weeks.

MBSR(BC) intervention

The MBSR(BC) intervention used in this study consisted of three processes: (i) educational material, (ii) practice of meditation in group meetings and homework assignments, and (iii) group processes related to barriers in the practice of meditation, application of mindfulness in daily situations, and supportive interaction between group members. BCS received training in four types of meditation techniques: (i) sitting meditation, (ii) body scan, (iii) gentle hatha yoga, and (iv) walking meditation. Participants met weekly for a 2-hr session over a duration of 6 weeks.

UC

The UC group consisted of standard post-treatment clinic visits. Participants were asked to refrain from enrolling in an MBSR program during the study period. Individuals randomized to UC were waitlisted and offered the MBSR(BC) program upon completion.

Demographic and clinical history measures

Demographics and clinical history

Standard socioeconomic demographic data, including age, gender, ethnicity, highest level of education completed, marital status, income status, and employment status, were collected at baseline and updated at 6 and 12 weeks. In addition, standard clinical history data on cancer diagnosis, such as diagnosis date, clinical stage, and treatment, were collected at baseline and updated at 6 and 12 weeks. As a component of clinical history, social history was gathered and included information on lifestyle health behaviors, use of alcohol and caffeine, smoking behavior, medications (including antidepressants, tamoxifen, and aromatase inhibitors), and exercise practices.

Outcome measures

Outcomes chosen for this study were based on the outcomes studied in Lengacher et al. [10].

Psychological symptoms

Depression was measured using the Center for Epidemiological Studies Depression Scale with a reported coefficient alpha reliability of 0.92 for breast cancer subjects [38, 39]. State anxiety was measured by the State Anxiety Inventory, and internal consistency reliability was 0.95 [40]. Perceived stress was measured by the Perceived Stress Scale, and internal consistency reliability ranged from 0.84 to 0.86 [41].

Physical symptoms

Fatigue was measured by the Fatigue Symptom Inventory [42]. The seven-item interference subscale had excellent internal consistency ($\alpha > 0.90$). Test–retest reliability over 3- to 12-week intervals among cancer patients was also favorable ($r = 0.35–0.75$). Pain was measured by the Brief Pain Inventory (BPI) that contained nine items that examined pain intensity and interference in patients [43]. Reliability coefficients for the BPI Severity and Interference scales were high, with reliability coefficients ranging from 0.82 to 0.95.

Quality of life

Quality of life was measured by the Medical Outcomes Studies short-form General Health Survey [44]. Estimates of internal consistency reliability ranged from 0.62 to 0.94, with the majority of scores exceeding 0.80. Test–retest reliability estimates ranged from 0.43 to 0.90.

Gene and SNP selection

Based on an extensive literature search performed by a molecular epidemiologist (JYP), candidate genes and SNPs were chosen to represent variations of the genes involved in various pathways, including depression and cognitive function in breast cancer. Among total 163 SNPs from 53 genes identified, 10 SNPs from eight genes were selected for this study, based on their significant associations with the efficacy of MBSR, cognitive function, depression, or known biological impacts on gene transcription or protein activity [23, 45–59]. We selected 10 SNPs in eight genes: rs1800497 in *ANKK1*, rs429358 in *APOE*, rs6265 in *BDNF*, rs4680 in *COMT*, rs6277 in *DRD2*, rs6313, rs6314 and rs4941573 in *HTR2A*, rs1801133 in *MTHFR,* and rs16965628 in *SLC6A4*.

Genotyping

"Genotype" refers to the genetic makeup, thus the alleles or variants of a gene. Each human has two

alleles at a gene, with one allele from each parent. A pair of alleles represents the genotype of a specific gene. Because each gene has two alleles, each human can have three possible genotypes at each gene: normal, mixed, and polymorphic. A genotype is described in this study as normal/polymorphic if it has two major/minor identical alleles and as mixed if the two alleles are different. Five milliliters of blood was drawn for the genotyping analysis. Genomic DNA was extracted from peripheral blood leukocytes using the Qiagen DNA extraction kit (Qiagen, Valencia, CA) with modifications. Ten candidate SNPs in eight genes were genotyped using the TaqMan allele discrimination polymerase chain reaction assay as described in previous studies [23].

Statistical methods

First, the distributions of all SNPs were examined to determine the prevalence of homozygous (e.g., AA or GG) or heterozygous genotypes. Polymorphisms were then compared across study assignment, race, and ethnicity using chi-square test or Fisher's Exact Test to assess any possible group differences in prevalence. The Hardy–Weinberg Equilibrium test was performed for genotype data (Table 1).

The next stage of the analysis included an examination of the relationships between SNPs, MBSR, and improvement of psychological and physical symptoms. Linear mixed models were used to estimate the effects of MBSR(BC) and genotype over three time points. The key focus of this study was the three-way interaction between MBSR(BC), genotype, and time (treated as a continuous variable). SNPs were treated as ordinal variables (e.g., AA = 1, AG = 2, GG = 3), and the three time points were baseline, 6 weeks, and 12 weeks. These models assumed an unstructured covariance matrix.

Two SNPs in HTR2A (rs6313 and rs4941573) were highly correlated ($r = -0.94$). As a result, only rs6313 was analyzed. Although the nine remaining SNPs were chosen deliberately, these analyses were not hypothesis driven. Rather, they were used to explore SNPs that might modify the effects of MBSR(BC). With nine SNPs and seven outcome measures, we examined 72 possible interactions. This large number of tests greatly increased the potential for type 1 error. Although the Adaptive Holm procedure was used to correct for multiple comparisons, we decided that effect sizes, rather than p values alone, should be used for making decisions about the reproducibility of our results [66]. The general linear model was used to calculate semipartial eta-squared effect sizes for each interaction. General rules of thumb for semipartial eta-squared are that effect sizes 0.01 or greater are considered small, 0.06 or greater are considered medium, and 0.14 or greater are considered large [67]. SAS version 9.4 was used for all statistical tests and multiple comparisons testing.

Table 1 | Characteristics of candidate single-nucleotide polymorphisms (SNPs; White participants; $N = 161$)

Gene	SNP ID	Allele (minor/major)	Change	Poly/HT/WT MBSR	Poly/HT/WT UC	HWE	Biological role
ANKK1[a]	rs1800497	A/G	Glu713Lys	4/31/43	2/21/60	1.00	Cognitive function ([12])
APOE[a]	rs429358	C/T	Cys156Arg	3/24/51	2/19/62	0.92	Cognitive function ([35, 12])
BDNF[a]	rs6265	T/C	Val66Met	3/29/46	2/23/58	0.94	Depression and cognitive impairment ([33, 60, 61])
COMT[a]	rs4680	G/A	Val158met	13/40/25	21/38/24	0.99	Pain ([37])
DRD2[a]	rs6277	G/A	Pro319Pro	20/34/24	13/51/19	0.90	Addictive behaviors and depression ([29, 62, 63])
HTR2A	rs6313	A/G	Ser34Ser	15/37/27	18/36/29	0.77	Depression and cognitive dysfunction ([32, 64])
HTR2A[a]	rs6314	A/G	His452Asn	0/12/66	2/11/70	0.88	
HTR2A[a]	rs4941573	G/A	Intron	17/33/27	18/35/30	0.86	
MTHFR[a]	rs1801133	C/T	Ala222Asp	6/38/34	13/40/30	0.79	Cognitive impairment and depression ([31, 65])
SLC6A4[a]	rs16965628	C/G	Intron	1/11/66	1/8/74	0.73	Depression and pain ([28, 30])

MBSR Mindfulness-Based Stress Reduction; *UC* usual care; *WT* wild type; *HT* heterozygous; *Poly* polymorphic; *HWE* Hardy-Weinberg equilibrium; *HWE* Hardy-Weinberg equilibrium.
[a]SNPs that were further analyzed for interactions with MBSR(BC).

RESULTS

Participant characteristics

For all SNPs, differences in the polymorphism prevalence between MBSR(BC) and UC groups were not statistically significant. However, differences of genotype distribution were observed by race. For example, the prevalence of rs4680 in COMT amongst Black participants was 0% AA, 44% AG, and 56% GG, compared to 30% AA, 49% AG, and 21% GG amongst White participants (p = 0.002). Due to differential genotype distribution by race (n = 24), non-White participants were removed from the analyses, and therefore only participants who self-identified as White were included in the MBSR(BC) by genotype analyses, leaving a sample size of 161. The mean age of these participants was 58 ± 9.3 years old. Participants were predominantly married (71%), and nearly half had a college degree (47%). Clinically, the majority of participants (73%) were diagnosed with stage I or II breast cancer. More than half of participants (58%) had a mastectomy, and some received adjuvant therapy consisting of chemotherapy (13%), radiotherapy (26%), or both (31%). The median time since cancer treatment was slightly <6 months (176 days). Selected demographic and clinical characteristics are described in Table 2.

MBSR(BC) and genotype interactions

The brief biological role, location, and genotype distributions of SNPs are presented in Table 1. Genotype distribution for all SNPs followed Hardy–Weinberg equilibrium (Table 1). Results from a series of 2 (MBSR[BC] vs. UC) by 3 (genotype) by 3 (time points) linear mixed models demonstrated four SNPs were statistically significant modifiers of MBSR(BC) effects (p < .05). These included rs6314_HTR2A (p = 0.04) and rs429358_APOE (p = 0.002) with pain. After corrections for multiple comparisons, only the latter remained statistically significant (p = 0.006). Although generally small, the pattern of effects told a broader story than the statistical significance by itself. Over the seven outcome measures, three SNPs had at least two effects that were of small effect size (semipartial $\eta^2 \geq 0.01$): rs429358_APOE (three effects), rs6277_DRD2 (three effects), and rs4680_COMT (two effects). Figures 1–3 provide a visual depiction of the largest effect from each of these three SNPs. Overall, the largest effect was a medium effect size (semipartial η^2 = 0.07) for the moderating effect of rs429358_APOE on pain severity.

For each of these three SNPs, we examined the pattern of the effect. For rs6277_DRD2 (three outcomes), results were mixed, and they seemed to be due to improvement in individuals with polymorphic genotype of the UC group, rather than differences in the MBSR(BC) group; Fig. 1 exemplifies this pattern. Across all outcomes for rs429358_APOE, patients with mixed genotype in the MBSR(BC) group experienced greater improvement compared with patients with normal genotype (there were very few CC patients); Fig. 2 demonstrates this interaction.

In addition, the results for rs4680_COMT were highly consistent. Across all outcomes, patients with polymorphic genotype demonstrated the most improvement in the MBSR(BC) group, with patients with normal genotype showing the least improvement, and patients with mixed genotype falling in-between; Fig. 3 visually depicts this pattern. Table 3 depicts the effect sizes, statistical significance, and favored allele across SNPs and outcomes.

DISCUSSION

The results of this study suggest the possibility that individual genotype differences may relate to the response to MBSR(BC) response in BCS. Three SNPs emerged as having noticeable effects across multiple outcomes. Specifically, rs429358 in APOE had three effects that were equal to or greater than semipartial η^2 of 0.01; two of the largest effect in the entire study (pain severity = 0.07) which also was the only statistically significant MBSR(BC) by time by genotype interactions after correcting for multiple comparisons (one of the pain measures); and all results in the same pattern (favoring CT over TT). APOE plays a major role in brain networks [68, 69], and APOE SNPs, including rs429358, are the most investigated for risk of brain diseases [70–72]. Specifically, the nonsynonymous SNP rs429358 causes an amino acid substitution from Cys to Arg at codon 130, affecting brain networks [34]. Although APOE is one of the most highly expressed proteins in the brain [73], biological roles of APOE have not been completely investigated. Our results suggest that rs429358 may be inversely related to improvement effects in response to the MBSR(BC) intervention.

The SNP rs4680 in COMT had two effects that were greater than semipartial η^2 of 0.01, and all results favoring polymorphic genotype over mixed and normal genotype. Previous studies examining the association of rs4680 in COMT have focused predominantly on depression. Recent studies have indicated that rs4680 is consistently associated with brain network functioning [74, 75]. The nonsynonymous SNP rs4680 causes an amino acid substitution from Val to Met at codon 158 of COMT, resulting in three to four times lower COMT activity than an amino acid substitution with the Val or G allele. Lowered COMT activity leads to reduced dopamine levels in postsynaptic neurons [76]. Therefore, it is biologically plausible that individuals with polymorphic allele (Met or A) demonstrated less improvement than patients with homozygous Val or G allele. Although modest in magnitude, the consistency of these results provides support for further investigation.

Table 2 | Demographic characteristics by random assignment

Demographic characteristics	All (N = 161)	UC (n = 83)	MBSR(BC) (n = 78)	p Value
Age in years (mean ± *SD*)	58.2 ± 9.3	58.3 ± 8.5	58.1 ± 10.1	.89
Marital status (%)				.83
Married	71 (114)	70 (58)	72 (56)	
Single	10 (16)	11 (9)	9 (7)	
Widowed	14 (22)	15 (12)	13 (10)	
Divorced	3 (5)	4 (3)	4 (3)	
Highest level of education (%)				.86
High school or less	19 (30)	19 (16)	18 (14)	
Some college or vocational	34 (55)	36 (30)	32 (25)	
College graduate and above	47 (76)	45 (37)	50 (39)	
Current employment status (%)				.59
Employed ≥ 32 hr per week	26 (41)	25 (21)	26 (20)	
Employed <32 hr per week	13 (21)	16 (13)	10 (8)	
Retired	35 (57)	31 (26)	40 (31)	
Medical leave/disabled	7 (11)	6 (5)	8 (6)	
Other	20 (31)	20 (18)	16 (13)	
Annual income (%)				.90
<$10,000	11 (18)	11 (9)	12 (9)	
$10,000 to <$20,000	16 (26)	16 (13)	17 (13)	
$20,000 to <$40,000	20 (32)	23 (19)	17 (13)	
$40,000 to <$80,000	30 (48)	27 (22)	34 (26)	
$80,000 to <$100,000	8 (13)	9 (7)	8 (6)	
$100,000 or more	14 (22)	15 (12)	13 (10)	
Clinical characteristics				
Stage (%)				.82
0	12 (19)	13 (11)	10 (8)	
I	39 (62)	39 (32)	39 (30)	
II	34 (55)	31 (26)	37 (29)	
III	16 (25)	17 (14)	14 (11)	
Type of surgery (% mastectomy)	58 (93)	60 (50)	55 (43)	.53
Cancer treatment				.95
Chemo only	13 (21)	15 (12)	12 (9)	
Radiation only	26 (42)	25 (21)	27 (21)	
Chemo and radiation	31 (50)	31 (26)	31 (24)	
No chemo or radiation	30 (48)	29 (24)	31 (24)	
Time since cancer treatment quartiles (%)				
<86 days	21 (33)	24 (20)	17 (13)	.10
86–176 days	24 (39)	23 (19)	26 (20)	
177–340 days	29 (46)	34 (28)	23 (18)	
>340 days	27 (43)	19 (16)	35 (27)	

p Values are derived from chi-square tests, with the exception of comparison of ages, which used a t test. *UC* usual care; *MBSR(BC)* Mindfulness-Based Stress Reduction for Breast Cancer.

These results provide preliminary understanding of genetic variability as it relates to complementary and alternative therapies for cancer patients. This is the first study to provide evidence that improvement in symptoms among BCS from an MBSR(BC) intervention may be contingent upon genetic profiles. These results may begin to identify BCS who might experience greater benefit from participation in an MBSR(BC) intervention designed to improve quality of life and psychological and physical symptoms. Our results correspond to the goals of precision medicine to optimize treatment efficacy by better understanding the outcomes of interventions among heterogeneous patient populations. This research contributes to translating MBSR as a tailored intervention that can be implemented in practice.

Limitations

Our study has a few limitations. First, the sample size was small (N = 161) and included women who received heterogeneous therapies, including chemotherapy and radiation treatment, which

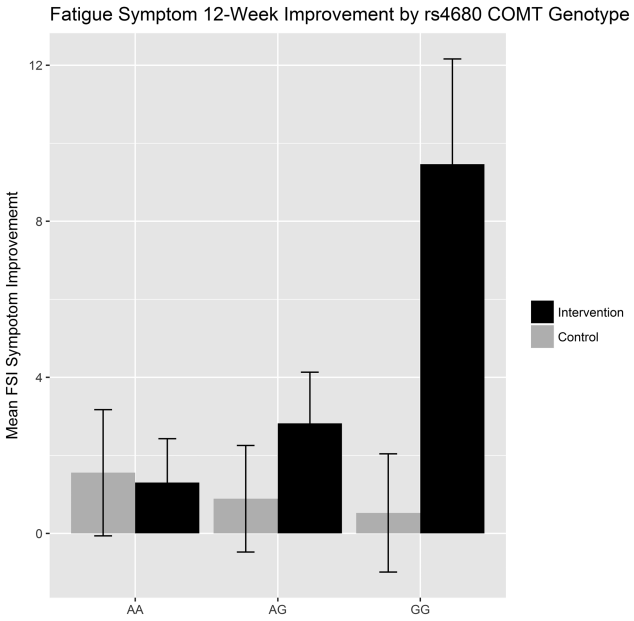

Fig. 1 | Mindfulness-Based Stress Reduction for Breast Cancer (MBSR[BC]) condition by rs6277 in *DRD2* genotype on fatigue symptom improvement ($p = .12$). Error bars represent standard error of the mean. *UC* usual care.

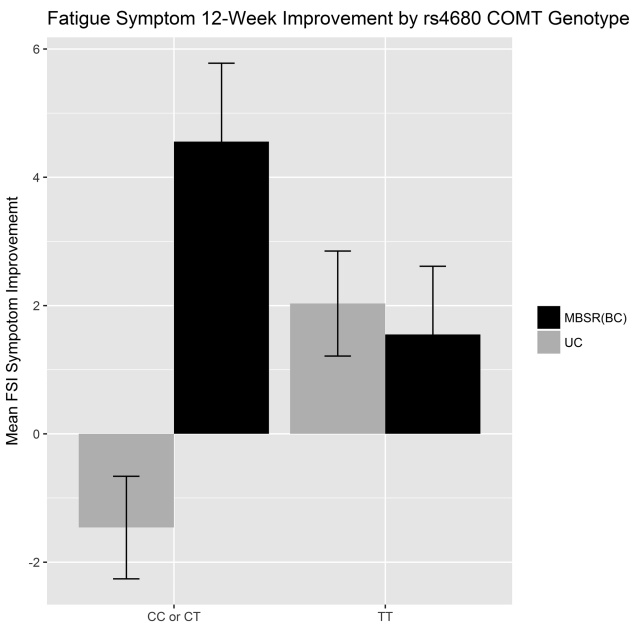

Fig. 2 | Mindfulness-Based Stress Reduction for Breast Cancer (MBSR[BC]) condition by rs429358 in *APOE* genotype on pain severity improvement ($p = .002$). Error bars represent standard error of the mean. *UC* usual care.

may significantly affect functioning. In addition, the small sample size did not permit examination of other potential confounders, such as race and cancer treatment regimens. Generally, genetic effects on mindfulness intervention tend to be small, and interaction effects need a much larger study to be detected. Although the effects observed in this study are small, they provide the foundation for future tests of patient-centered MBSR(BC) effects. We are more confident in the reproducibility of the rs429358 and rs4680 results. Due to the significant difference in genotype distribution among different populations and a relatively small proportion of our sample being non-White ($n = 11$), we constricted our analysis to include only White participants. Therefore, the results of this study may not be generalizable to non-White groups. Because different BCS racial groups suffer different levels of stress from cancer treatment, a large study with diverse racial and ethnic background is warranted. In addition, because participants entered the study after

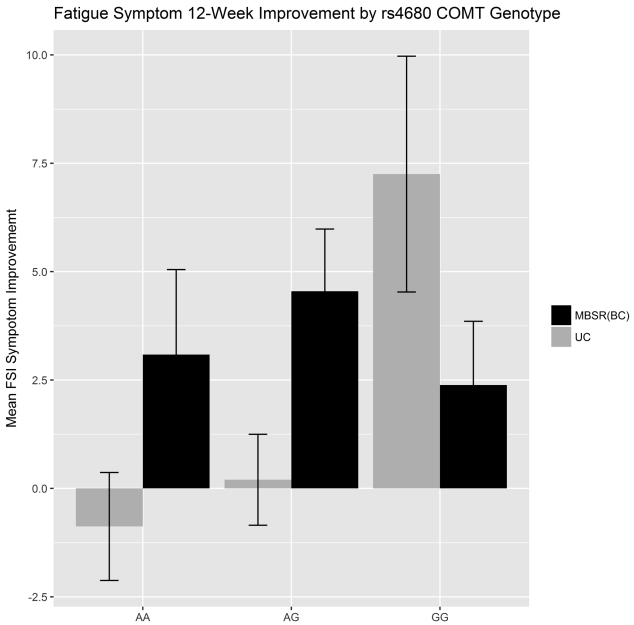

Fig. 3 | Mindfulness-Based Stress Reduction for Breast Cancer (MBSR[BC]) condition by rs4680 in *COMT* genotype on fatigue symptom improvement ($p = .08$). Error bars represent standard error of the mean. *UC* usual care.

Table 3 | Effect size, statistical significance, and pattern of genotype by Mindfulness-Based Stress Reduction for Breast Cancer (MBSR[BC]) interactions for each outcome variable

	rs6314_ HTR2A	rs1800497_ ANKK1	rs6277_ DRD2	rs6265_ BDNF	rs429358_ APOE	rs4680_ COMT	rs4941573_ HTR2A	rs1801133_ MTHFR	rs16965628_ SLC6A4
CESD-depression	–	–	0.01	0.02	0.03	–	–	–	–
STAI-anxiety	–	–	–	–	–	–	–	–	–
PSS-stress	–	–	–	–	–	–	–	–	–
CARS-fear of recurrence									
Overall	–	0.01	–	–	–	–	–	–	–
FSI-fatigue									
Symptoms	–	–	0.03	–	–	0.04	–	–	–
BPI-pain									
Severity	0.03	–	–	–	0.07**	0.02	–	–	–
SF36-quality of life									
General health	–	–	0.01	–	0.02	–	–	0.01	–
Favored allele			Inconsistent		C[a]	G			

Effect sizes represent the semipartial eta-squared derived from MBSR(BC) by genotype interactions on symptom improvement. Conventionally, semipartial eta-squared is considered small ≥0.01; medium ≥0.06; or large ≥0.14. *BPI* Brief Pain Inventory; *CESD* Center for Epidemiological Studies Depression Scale; *FSI* Fatigue Symptom Inventory; *PSS* Perceived Stress Scale; *CARS* Concerns About Recurrence Scale; *STAI* State-Trait Anxiety Inventory.

[a]Homozygous patients of this genotype were rare or nonexistent in our sample.

**$p < .01$ after multiple comparisons testing using the Adaptive Holm Procedure ([7]).

completion of treatment, we were unable to assess symptoms prior to breast cancer diagnosis and/or treatment. Therefore, it could not be determined whether the lower baseline existed prior to treatment. Furthermore, because the study was a randomized clinical trial among BCS, healthy controls were not included. As a result, our findings may not apply to the general population.

Implications

More research is needed to definitively identify BCS at risk for symptom decline and determine whether the genetic profiles of BCS affect the impact of specific interventions such as MBSR(BC). Eventually, these concepts may be used to develop personalized treatment programs tailored to the genetic profile of each patient as part of precision medicine, particularly for

those who did not show benefit from MBSR(BC) [77]. Further, recent advances in whole genome sequencing technologies and behavioral measurement methods may help to assess individual impacts of interventions or treatments based on their genetic profile. The technologies and methods used in precision medicine also may help to reveal molecular mechanisms for different responses to treatment and intervention among patients with different genetic backgrounds.

Research and practice in prevention, treatment, and recovery from cancer have much to gain from continued advances in precision medicine. More research is needed on precision medicine to facilitate translation to clinical practice. After critical SNPs for effective intervention are identified, these genetic profiles should be validated in independent population sets to be generalized.

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Compliance with Ethical Standards

Primary Data: This article and data are not under consideration for publication elsewhere nor have the findings been previously published.

Conflict of Interest: The authors have no conflicts to report.

Authors' Contributions: All of the authors have contributed substantially to the article's development and each has read and approved the current submission. The authors have full control of primary data, and scored data can be released upon request if needed; however, the raw data due to the institutional review board–approved submission will not permit the release of the data which include genetic information.

Ethical Approval: Guidelines for ethical conduct and report of research are met in this study. The study protocol was approved by the Institutional Review Board at the University of South Florida to ensure the ethical treatment of participants.

References

1. American Cancer Society. Cancer Facts & Figures 2017. 2017. Available at https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2017/cancer-facts-and-figures-2017.pdf. Accessibility verified August 2, 2017.
2. Howlader N, Noone AM, Krapcho M, et al. *SEER Cancer Statistics Review, 1975–2014*. Bethesda, MD: National Cancer Institute; 2017.
3. Berger AM, Gerber LH, Mayer DK. Cancer-related fatigue: Implications for breast cancer survivors. *Cancer*. 2012;118(suppl 8):2261–2269.
4. Dodd MJ, Cho MH, Cooper BA, Miaskowski C. The effect of symptom clusters on functional status and quality of life in women with breast cancer. *Eur J Oncol Nurs*. 2010;14(2):101–110.
5. Hall DL, Mishel MH, Germino BB. Living with cancer-related uncertainty: Associations with fatigue, insomnia, and affect in younger breast cancer survivors. *Support Care Cancer*. 2014;22(9):2489–2495.
6. Lengacher CA, Reich RR, Post-White J, et al. Mindfulness based stress reduction in post-treatment breast cancer patients: An examination of symptoms and symptom clusters. *J Behav Med*. 2012;35(1):86–94.
7. Fu OS, Crew KD, Jacobson JS, et al. Ethnicity and persistent symptom burden in breast cancer survivors. *J Cancer Surviv*. 2009;3(4):241–250.
8. Wu HS, Harden JK. Symptom burden and quality of life in survivorship: A review of the literature. *Cancer Nurs*. 2015;38(1):E29–E54.
9. Carlson LE, Doll R, Stephen J, et al. Randomized controlled trial of mindfulness-based cancer recovery versus supportive expressive group therapy for distressed survivors of breast cancer. *J Clin Oncol*. 2013;31(25):3119–3126.
10. Lengacher CA, Reich RR, Paterson CL, et al. Examination of broad symptom improvement resulting from mindfulness-based stress reduction in breast cancer survivors: A randomized controlled trial. *J Clin Oncol*. 2016;34(24):2827–2834.
11. Lengacher CA, Johnson-Mallard V, Post-White J, et al. Randomized controlled trial of mindfulness-based stress reduction (MBSR) for survivors of breast cancer. *Psychooncology*. 2009;18(12):1261–1272.
12. Lengacher CA, Reich RR, Paterson CL, et al. The effects of mindfulness-based stress reduction on objective and subjective sleep parameters in women with breast cancer: A randomized controlled trial. *Psychooncology*. 2015;24(4):424–432.
13. Morandi A, Bonnefond A, Lobbens S, et al. Associations between type 2 diabetes-related genetic scores and metabolic traits, in obese and normal-weight youths. *J Clin Endocrinol Metab*. 2016;101(11):4244–4250.
14. Percival N, George A, Gyertson J, et al. The integration of BRCA testing into oncology clinics. *Br J Nurs*. 2016;25(12):690–694.
15. Molina-Moya B, Kazdaglis G, Lacoma A, et al. Evaluation of genoFlow DR-MTB array test for detection of Rifampin and Isoniazid resistance in Mycobacterium tuberculosis. *J Clin Microbiol*. 2016;54(4):1160–1163.
16. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365–376.
17. Marcus PM, Pashayan N, Church TR, et al. Population-based precision cancer screening: A symposium on evidence, epidemiology, and next steps. *Cancer Epidemiol Biomarkers Prev*. 2016;25(11):1449–1455.
18. Wickramage I, Tennekoon KH, Ariyaratne MA, Hewage AS, Sundralingam T. CYP2D6 polymorphisms may predict occurrence of adverse effects to tamoxifen: A preliminary retrospective study. *Breast Cancer (Dove Med Press)*. 2017;9:111–120.
19. Mirnezami R, Nicholson J, Darzi A. Preparing for precision medicine. *N Engl J Med*. 2012;366(6):489–491.
20. Enge S, Mothes H, Fleischhauer M, Reif A, Strobel A. Genetic variation of dopamine and serotonin function modulates the feedback-related negativity during altruistic punishment. *Sci Rep*. 2017;7(1):2996.
21. Doan RN, Bae BI, Cubelos B, et al.; Homozygosity Mapping Consortium for Autism. Mutations in human accelerated regions disrupt cognition and social behavior. *Cell*. 2016;167(2):341–354.
22. Thorgeirsson TE, Steinberg S, Reginsson GW, et al. A rare missense mutation in CHRNA4 associates with smoking behavior and its consequences. *Mol Psychiatry*. 2016;21(5):594–600.
23. Lengacher CA, Reich RR, Kip KE, et al. Moderating effects of genetic polymorphisms on improvements in cognitive impairment in breast cancer survivors participating in a 6-week mindfulness-based stress reduction program. *Biol Res Nurs*. 2015;17(4):393–404.
24. Gonzalez BD, Jim HS, Booth-Jones M, et al. Course and predictors of cognitive function in patients with prostate cancer receiving androgen-deprivation therapy: A controlled comparison. *J Clin Oncol*. 2015;33(18):2021–2027.
25. Boots E, Schultz S, Clark L, et al. BDNF Val66Met predicts cognitive decline in the Wisconsin registry for Alzheimer's prevention. *Neurology*. 2017;88(22):2096–2103.
26. Doong SH, Dhruva A, Dunn LB, et al. Associations between cytokine genes and a symptom cluster of pain, fatigue, sleep disturbance, and depression in patients prior to breast cancer surgery. *Biol Res Nurs*. 2015;17(3):237–247.
27. Shi Q, Wang XS, Li G, et al. Racial/ethnic disparities in inflammatory gene single-nucleotide polymorphisms as predictors of a high risk for symptom burden in patients with multiple myeloma 1 year after diagnosis. *Cancer*. 2015;121(7):1138–1146.
28. Schillani G, Martinis E, Capozzo MA, et al. Psychological response to cancer: Role of 5-HTTLPR genetic polymorphism of serotonin transporter. *Anticancer Res*. 2010;30(9):3823–3826.
29. Zhang W, Cao Y, Wang M, Ji L, Chen L, Deater-Deckard K. The Dopamine D2 Receptor Polymorphism (DRD2 TaqIA) interacts with maternal parenting in predicting early adolescent depressive symptoms: Evidence of differential susceptibility and age differences. *J Youth Adolesc*. 2015;44(7):1428–1440.
30. Wesmiller SW, Bender CM, Sereika SM, et al. Association between serotonin transport polymorphisms and postdischarge nausea and vomiting in women following breast cancer surgery. *Oncol Nurs Forum*. 2014;41(2):195–202.
31. Jiang W, Xu J, Lu XJ, Sun Y. Association between MTHFR C677T polymorphism and depression: A meta-analysis in the Chinese population. *Psychol Health Med*. 2016;21(6):675–685.
32. Kurita GP, Ekholm O, Kaasa S, Klepstad P, Skorpen F, Sjogren P. Genetic variation and cognitive dysfunction in opioid-treated patients with cancer. *Brain Behav*. 2016;6(7):e004471.
33. Ng T, Teo SM, Yeo HL, et al. Brain-derived neurotrophic factor genetic polymorphism (rs6265) is protective against chemotherapy-associated cognitive impairment in patients with early-stage breast cancer. *Neuro Oncol*. 2016;18(2):244–251.
34. Su YY, Liang X, Schoepf UJ, et al. APOE polymorphism affects brain default mode network in healthy young adults: A STROBE article. *Medicine (Baltimore)*. 2015;94(52):e1734.

35. Koleck TA, Bender CM, Sereika SM, et al. Apolipoprotein E genotype and cognitive function in postmenopausal women with early-stage breast cancer. *Oncol Nurs Forum.* 2014;41(6):E313–E325.
36. Athanasoulia AP, Sievers C, Uhr M, Ising M, Stalla GK, Schneider HJ. The effect of the ANKK1/DRD2 Taq1A polymorphism on weight changes of dopaminergic treatment in prolactinomas. *Pituitary.* 2014;17(3):240–245.
37. Yao P, Ding YY, Wang ZB, Ma JM, Hong T, Pan SN. Effect of gene polymorphism of COMT and OPRM1 on the preoperative pain sensitivity in patients with cancer. *Int J Clin Exp Med.* 2015;8(6):10036–10039.
38. Hann D, Winter K, Jacobsen P. Measurement of depressive symptoms in cancer patients: Evaluation of the Center for Epidemiological Studies Depression Scale (CES-D). *J Psychosom Res.* 1999;46(5):437–443.
39. Radloff L. The CES-D scale: A self-report depression scale for researching the general population. *Appl Psychol Meas.* 1977;1(3):385–401.
40. Spielberger C, Gorsuch R, Luschene R. *Manual for the State-Trait Anxiety Inventory.* Palo Alto, CA: Consulting Psychologists; 1983.
41. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav.* 1983;24(4):385–396.
42. Hann DM, Jacobsen PB, Azzarello LM, et al. Measurement of fatigue in cancer patients: Development and validation of the Fatigue Symptom Inventory. *Qual Life Res.* 1998;7(4):301–310.
43. Keller S, Bann CM, Dodd SL, Schein J, Mendoza TR, Cleeland CS. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. *Clin J Pain.* 2004;20(5):309–318.
44. Ware JH, Kosinski M, Keller M. *SF-36 Physical and Mental Health Summary Scales, a User's Manual.* 2nd ed. Boston, MA: The Health Institute; 1994.
45. Chen J, Lipska BK, Halim N, et al. Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): Effects on mRNA, protein, and enzyme activity in postmortem human brain. *Am J Hum Genet.* 2004;75(5):807–821.
46. Fisher PM, Holst KK, Adamsen D, et al. BDNF Val66met and 5-HTTLPR polymorphisms predict a human in vivo marker for brain serotonin levels. *Hum Brain Mapp.* 2015;36(1):313–323.
47. Hirvonen M, Laakso A, Någren K, Rinne JO, Pohjalainen T, Hietala J. C957T polymorphism of the dopamine D2 receptor (DRD2) gene affects striatal DRD2 availability in vivo. *Mol Psychiatry.* 2004;9(12):1060–1061.
48. Martin J, Cleak J, Willis-Owen SA, Flint J, Shifman S. Mapping regulatory variants for the serotonin transporter gene based on allelic expression imbalance. *Mol Psychiatry.* 2007;12(5):421–422.
49. Ni X, Bismil R, Chan K, et al. Serotonin 2A receptor gene is associated with personality traits, but not to disorder, in patients with borderline personality disorder. *Neurosci Lett.* 2006;408(3):214–219.
50. Polesskaya OO, Sokolov BP. Differential expression of the "C" and "T" alleles of the 5-HT2A receptor gene in the temporal cortex of normal individuals and schizophrenics. *J Neurosci Res.* 2002;67(6):812–822.
51. Ponce G, Pérez-González R, Aragüés M, et al. The ANKK1 kinase gene and psychiatric disorders. *Neurotox Res.* 2009;16(1):50–59.
52. Prada D, Colicino E, Power MC, et al. Influence of multiple APOE genetic variants on cognitive function in a cohort of older men—Results from the Normative Aging Study. *BMC Psychiatry.* 2014;14:223.
53. Swagell CD, Lawford BR, Hughes IP, et al. DRD2 C957T and TaqIA genotyping reveals gender effects and unique low-risk and high-risk genotypes in alcohol dependence. *Alcohol Alcohol.* 2012;47(4):397–403.
54. Ueland PM, Hustad S, Schneede J, Refsum H, Vollset SE. Biological and clinical implications of the MTHFR C677T polymorphism. *Trends Pharmacol Sci.* 2001;22(4):195–201.
55. Wagner M, Schuhmacher A, Schwab S, Zobel A, Maier W. The His452Tyr variant of the gene encoding the 5-HT2A receptor is specifically associated with consolidation of episodic memory in humans. *Int J Neuropsychopharmacol.* 2008;11(8):1163–1167.
56. Merriman JD, Aouizerat BE, Cataldo JK, et al. Association between an interleukin 1 receptor, type I promoter polymorphism and self-reported attentional function in women with breast cancer. *Cytokine.* 2014;65(2):192–201.
57. Ng T, Chan M, Khor CC, Ho HK, Chan A. The genetic variants underlying breast cancer treatment-induced chronic and late toxicities: A systematic review. *Cancer Treat Rev.* 2014;40(10):1199–1214.
58. Koleck TA, Bender CM, Sereika SM, et al. Polymorphisms in DNA repair and oxidative stress genes associated with pre-treatment cognitive function in breast cancer survivors: An exploratory study. *Springerplus.* 2016;5(1):422.
59. Bal JK, Beuvier T, Vignaud G, et al. Swelling of poly(n-butyl methacrylate) films exposed to supercritical carbon dioxide: A comparative study with polystyrene. *Langmuir.* 2016;32(7):1716–1722.
60. Dooley LN, Ganz PA, Cole SW, et al. Val66Met BDNF polymorphism as a vulnerability factor for inflammation-associated depressive symptoms in women with breast cancer. *J Affect Disord.* 2016;197:43–50.
61. Kang HJ, Kim JM, Kim SY, et al. A longitudinal study of BDNF promoter methylation and depression in breast cancer. *Psychiatry Investig.* 2015;12(4):523–531.
62. Ma Y, Wang M, Yuan W, et al. The significant association of Taq1A genotypes in DRD2/ANKK1 with smoking cessation in a large-scale meta-analysis of Caucasian populations. *Transl Psychiatry.* 2015;5:e686.
63. Reyes-Gibby CC, Yuan C, Wang J, et al. Gene network analysis shows immune-signaling and ERK1/2 as novel genetic markers for multiple addiction phenotypes: alcohol, smoking and opioid addiction. *BMC Syst Biol.* 2015;9(25).
64. Bielinski M, Tomaszewska M, Jaracz M, et al. The polymorphisms in serotonin-related genes (5-HT(2)A and SERT) and the prevalence of depressive symptoms in obese patients. *Neurosci Lett.* 2015;586:31–35.
65. Stanger O, Fowler B, Piertzik K, et al. Homocysteine, folate and vitamin B12 in neuropsychiatric diseases: review and treatment recommendations. *Expert Rev Neurother.* 2009;9:1393–1412.
66. Hochberg Y, Benjamini Y. More powerful procedures for multiple significance testing. *Stat Med.* 1990;9(7):811–818.
67. Miles J, Shevlin M. *Applying Regression and Correlation: A Guide for Students and Researchers.* London, UK: Sage Publications; 2001.
68. Lahiri DK, Sambamurti K, Bennett DA. Apolipoprotein gene and its interaction with the environmentally driven risk factors: Molecular, genetic and epidemiological studies of Alzheimer's disease. *Neurobiol Aging.* 2004;25(5):651–660.
69. Li J, Zhang F, Wang Y, et al. Association between ε2/3/4, promoter polymorphism (-491A/T, -427T/C, and -219T/G) at the apolipoprotein E gene, and mental retardation in children from an iodine deficiency area, China. *Biomed Res Int.* 2014;2014:236702.
70. Morley KI, Montgomery GW. The genetics of cognitive processes: Candidate genes in humans and animals. *Behav Genet.* 2001;31(6):511–531.
71. Schiepers OJ, Harris SE, Gow AJ, et al. APOE E4 status predicts age-related cognitive decline in the ninth decade: Longitudinal follow-up of the Lothian Birth Cohort 1921. *Mol Psychiatry.* 2012;17(3):315–324.
72. Xin XY, Ding JQ, Chen SD. Apolipoprotein E promoter polymorphisms and risk of Alzheimer's disease: Evidence from meta-analysis. *J Alzheimers Dis.* 2010;19(4):1283–1294.
73. Elliott DA, Kim WS, Jans DA, Garner B. Apoptosis induces neuronal apolipoprotein-E synthesis and localization in apoptotic bodies. *Neurosci Lett.* 2007;416(2):206–210.
74. Schacht JP. COMT val158met moderation of dopaminergic drug effects on cognitive function: A critical review. *Pharmacogenomics J.* 2016;16(5):430–438.
75. Liao YJ, Jiang JR, Jin SQ. The association between COMT Val158Met polymorphism and migraine risk: A meta-analysis. *Cephalalgia.* 2017;37(6):592–598.
76. Egan MF, Goldberg TE, Kolachana BS, et al. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proc Natl Acad Sci USA.* 2001;98(12):6917–6922.
77. Grady PA, Gough LL. Nursing Science: Claiming the Future. *J Nurs Scholarsh.* 2015;47(6):512–521.