Translational Genomic Research: The Association between Genetic Profiles and Cognitive Functioning or Cardiac Function Among Breast Cancer Survivors Completing Chemotherapy

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Abstract

Introduction: Emerging evidence suggests that Chemotherapy (CT) treated breast cancer survivors (BCS) who have "risk variants" in genes may be more susceptible to cognitive impairment (CI) and/or poor cardiac phenotypes. The objective of this preliminary study was to examine whether there is a relationship between genetic variants and objective/subjective cognitive or cardiac phenotypes. **Methods and Analysis:** BCS were recruited from Moffitt Cancer Center, Morsani College of Medicine, AdventHealth Tampa and Sarasota Memorial Hospital. Genomic DNA were collected at baseline for genotyping analysis. A total of 16 single nucleotide polymorphisms (SNPs) from 14 genes involved in cognitive or cardiac function were evaluated. Three genetic models (additive, dominant, and recessive) were used to test correlation coefficients between genetic variants and objective/subjective measures of cognitive functioning and cardiac outcomes (heart rate, diastolic blood pressure, systolic blood pressure, respiration rate, and oxygen saturation). **Results:** BCS (207 participants) with a mean age of 56 enrolled in this study. The majority were non-Hispanic white (73.7%), married (63.1%), and received both CT and radiation treatment (77.3%). Three SNPs in genes related to cognitive functioning (rs429358 in *APOE*, rs1800497 in *ANKK1*, rs10119 in *TOMM40*) emerged with the most consistent significant relationship with cognitive outcomes. Among five candidate SNPs related to cardiac functioning, rs8055236 in *CDH13* and rs1801133 in *MTHER* emerged with potential significant relationships with cardiac phenotype. **Conclusions:** These preliminary results provide initial targets to further examine whether BCS with specific genetic profiles may preferentially benefit from interventions designed to improve cognitive and cardiac functioning following CT.

Keywords

genetic, cognitive dysfunction, cardiac function, chemotherapy, cancer survivors, breast cancer

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An estimated number of 281,550 new cases of invasive breast cancer is predicted among women in the United States in 2021 (Siegel et al., 2021). For these women, although chemotherapy (CT) increases the survival rate (D. Chen et al., 2021), CT-associated cognitive impairment (CI) was found in 13–70% of breast cancer survivors (BCS), (Tao et al., 2017) and continues years beyond treatment (Y. Chen et al., 2022; Ganz, 2012; Pullens et al., 2010; Yamada et al., 2010).

Chemotherapy treatment not only affects cognitive functioning in multiple ways (e.g., memory, processing speed) for

BCS, (Deprez et al., 2018; Jim et al., 2012; Pullens et al., 2010; Ren et al., 2019; Wefel et al., 2010), also affecting BCS's quality of life; (Xuan et al., 2017) and their ability to return to work, resulting in economic burdens and increased psychological stress (Mazanec et al., 2021; Munir et al., 2011; Wefel et al., 2010).

Objective and subjective measures of cognitive functioning were selected for this study. Currently, most research implements use of subjective measures due to the ease of obtaining the patients perception of their cognitive abilities. To be more precise in assessment of cognitive functioning, objective neuropsychological measures provide more validity and reliability in assessment of several cognitive domains, not provided by subjective assessments.

BCS often have ongoing symptoms, such as pain, fatigue, sleep disturbance, and depression, that vary between individuals with current evidence identifying one's genes may influence one's symptom experience (E. Boots et al., 2017; S. Doong et al., 2014). Recovery for BCS symptom experience (cognitive, psychological, and physical) may be enhanced if there is increased understanding and evidence explaining the relationships between one's genetic profile and their symptom experiences. This scientific evidence supports achieving the goals of precision medicine to tailor treatment plans for symptoms based on one's genetics to promote best health outcomes with minimal consequences (Mirnezami et al., 2012).

CT-induced cardiac dysfunction is a serious side effect of chemotherapy. This notorious side effect occurs ~10% of BCS with CT (Teske et al., 2018). However, individual variation of CT-induced cardiac dysfunction cannot be fully explained by known clinical risk factors. We hypothesized that genetic variants may provide better explanation. Also, we evaluated a role of genetic risk factors in CT-induced cardiac dysfunction among BCS.

Recent advances in molecular genomic technologies, and extensive genomic research identify risky genomic variations for disease predisposition, progression, and response of treatments. Current knowledge of genomic variation and mutations have been translated into clinical settings for prevention of disease and clinical treatments (Lee et al., 2020; Molina-Moya et al., 2016; Morandi et al., 2016; Percival et al., 2016). For example, BCS with SNPs in *CYP2D6* are found to be at an increased risk for adverse effect from the tamoxifen therapy and therefore, BCS with SNPs (rs28371725 and rs16947) in *CYP2D6* are to be treated with alternative therapies, such as aromatase inhibitors (Wickramage et al., 2017).

Emerging evidence suggests that genetic factors may influence CT-associated CI among BCS (Ahles et al., 2010; Chan et al., 2019; Park et al., 2019; Stewart et al., 2008; Tan et al., 2019; G. S. Yang et al., 2019). Individual patient genetic profiles may be associated with increased risk for long-term cognitive changes (Carroll et al., 2019; de Frutos-Lucas et al., 2020). Genetic variants in cognitive functioning pathways also may play a role in CT-associated CI. Previous evidence report that CT-treated BCS who have "risk variants" in Apo lipoprotein E (APOE) and catechol-o-methyl transferase (COMT) genes are more susceptible to cognitive dysfunction (Ahles et al., 2010; Buskbjerg et al., 2019; Carroll et al., 2019; Lengacher, Reich, Kip, et al., 2015; Stewart et al., 2008).

After an extensive review of the evidence, 12 SNPs in 11 candidate genes involved in cognitive functioning were selected and investigated for their role among breast cancer survivors. Additionally, we evaluated the potential role of five SNPs from four genes, involved in cardiac symptoms among BCS. Products of these genes considered receptors, carriers, transporters, and metabolic enzymes in various pathways. Gene variations in apolipoprotein E (*APOE*), brain-derived neurotrophic factor (*BDNF*), serotonin receptor 2A (*5HTR2A*), AK091365 (Davies et al., 2016; Rietveld et al., 2014), *AKAP6* (Andrews et al., 2017; Davies et al., 2015, 2016), *TOMM40* (Davies et al., 2015), *BCL11A* (Le Hellard et al., 2017), ankyrin repeat and kinase domain containing 1 (ANKK1) (Athanasoulia et al., 2014) and *APBA1* (Davies et al., 2016; Sloan et al., 2010) were previously related to cognitive function (Jiang et al., 2016; Koleck et al., 2014; Kurita et al., 2016; Ng et al., 2016; Schillani et al., 2010; Su et al., 2015; Zhang et al., 2015).

Further, SNPs in *CDH13* (Angelakopoulou et al., 2012; Bressler et al., 2010), *CXCL12* (Ansari et al., 2019; Spiller et al., 2020), *CDKN2B* (Hu et al., 2019; Trenkwalder et al., 2019), and methylenetetrahydrofolate reductase (*MTHFR*) (H. L. Yang et al., 2018) have been associated with cardiac function.

The purpose of this sub-analysis was to explore the relationship between SNPs in candidate genes and cognitive and cardiac functioning among BCS with previous CT. If we can identify initial targets for investigation, we can identify whether BCS with specific genetic profiles may preferentially benefit from interventions designed to enhance cognitive and cardiac functioning following CT. An overarching goal of this personalized medicine project is to tailor symptom-relief interventions based on genetic profiles of BCS.

Methods

Participants

Among 212 BCS who consented to participate in our R01 MBSR(BC) Trial, 207 completed the genetic analysis. The overarching purpose of the parent study was to evaluate the efficacy of the Mindfulness-Based Stress Reduction (BC) program compared to the Breast Cancer-Education Support (BCES) program or a usual care (UC) regimen for improving cognitive functioning among BCS, who received adjuvant chemotherapy, or chemotherapy and radiation. Data from this study were obtained at baseline, prior to the randomized intervention.

BCS were recruited from the Moffitt Cancer Center, USF Breast Health Program, AdventHealth Hospital, Tampa, Florida. Sarasota Memorial Hospital, Sarasota Florida, and

community groups. Primary inclusion criteria included women age 21 or older diagnosed with stage I, II, or III BC, completed CT or CT and radiation, within 5 years post-treatment, and met the screening criteria for CI with a positive response to 1 of 2 questions: 1) "Have you had difficulty in concentrating on things, like reading a newspaper or watching television; " and 2) "Have you had difficulty remembering things" (Montazeri et al., 1999). Exclusion criteria included severe psychiatric diagnosis (e.g., bipolar disorder), Stage 0 or Stage IV BC, history of another primary cancer diagnosis with the treatment of CT and/or radiation, metastatic cancer, current neurologic disorder, or a traumatic brain injury.

Study Design and Data Collection

Clinic nurses identified eligible BCS who were then approached by study recruiters. BCS who expressed interest in the study were invited to an orientation session where consent was obtained followed by baseline data collection. The assessment included obtaining 5 mL of blood or buccal (cheek) cell sample for genotyping analysis only at baseline, along with administration of objective neuropsychological assessments and subjective cognitive, clinical treatment, and demographic data. For cardiac data collection, among 212 patients, 28 BCS only participated.

Measurements

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 following orientation. Standard clinical history data on cancer diagnosis, diagnosis date, clinical stage, and treatment were collected as well.

Cognitive performance. Cognitive performance tests were selected based on previous research among cancer patients (Booth-Jones et al., 2005; Jacobs et al., 2007) demonstrating reliability and validity with published normative data for adults (Booth-Jones et al., 2005; Jacobs et al., 2007).

Objective Cognitive Performance. Memory was assessed using tests of visuospatial, verbal, and logical memory: 1) *Visuospatial memory* was measured by the Brief Visuospatial Memory Test-Revised (BVMT-R) alpha reliability (0.96–0.97) (Benedict, 1997); 2) *Verbal memory* was measured by the Hopkins Verbal Learning Test-Revised (HVLT-R) alpha reliability (0.76–0.86) (Benedict et al., 1998; Brandt, 1991); and 3) *Logical memory* was measured by the Logical Memory I and II subscales from the Wechsler Memory Scale-IV (WMS-IV) alpha reliability (0.70–0.90) (D. Wechsler, 2009). Attention/Concentration was measured using the Digit Span subtest of the WAIS-IV, alpha reliability (0.90) (D. Wechsler, 2008), and Part 1 of the Color Trails Test (CTT-1) alpha reliability (0.64) (D'Elia et al., 1996; Maj et al., 1993). Executive functioning was measured by Part 2 of the Color Trails Test (CTT-2) alpha reliability (0.79) (D'Elia et al., 1996; Maj et al., 1993), and

Stroop Neuropsychological Screening Test (SNST) alpha reliability (0.73–0.89) (Trenerry et al., 1989). Verbal fluency was measured by the Controlled Oral Word Association Test (COWAT) alpha reliability (0.70) (Benton & Hamsher, 1989) and the Wechsler Test of Adult Reading (WTAR) alpha reliability (0.90–0.97) (Corporation, 2001).

Perceived cognitive performance. The Functional Assessment of Cancer Therapy–Cognitive Function (FACT-Cog) alpha reliability (0.82) was used to assess subjective change of everyday perceived cognitive performance (Wagner, L. I., Sweet, Butt, Lai, & Cella, 2009).

Cardiac measures. Measures of cardiovascular functioning included systolic and diastolic blood pressure, heart rate, respiratory rate, and oxygen saturation, which were collected at the baseline.

Genotyping

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, cognitive function, and cardiac phenotype in BC. Among total 208 SNPs from 58 genes identified, 16 SNPs from 14 genes were selected for this study, based on their significant associations with cognitive function and cardiac function (Bal et al., 2016; J. Chen et al., 2004; Fisher et al., 2015; Hirvonen et al., 2004; Koleck et al., 2016; Lengacher, Reich, Kip, et al., 2015; Lengacher, Reich, Paterson, et al., 2015; Martin et al., 2007; Merriman et al., 2014; Ng et al., 2014; Ni et al., 2006; Polesskaya & Sokolov, 2002; Ponce et al., 2009; Prada et al., 2014; Ueland et al., 2001; M. Wagner et al., 2008).

Analysis

Genotyping Analysis

"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 (Hughes et al., 2021). 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 were drawn for the genotyping analysis. Genomic DNA was extracted from peripheral blood leukocytes or buccal cells using the Qiagen DNA extraction kit (Qiagen, Valencia, CA) with modifications.

Genetic Measurements

Multiple candidate SNPs involved in cognitive or cardiac function were selected based on previous research and

preliminary data. Genotyping methods were used as described for Moffitt's laboratory (Jim et al., 2012).

The distribution of genotype frequencies of candidate SNPs examined were tested for Hardy-Weinberg equilibrium (HWE) based on categories of race using an asymptotic chi-square test (1 degree of freedom) with a graphical summary or an exact test based on a multinomial distribution if the data are sparse. The HWE is a principle stating that the genetic variation in a population will remain constant from one generation to the next.

Statistical Analysis Plan

Wilcoxon rank sum test or Kruskal Wallis test was used to evaluate whether genetic factors were associated with cognitive or cardiac function. Because we tested multiple genes (each using three genetic models (additive, dominant, and recessive)) and multiple outcomes, we were cognizant of the potential for Type 1 error. Because of our relatively small sample and the anticipated small effect sizes, we did not want to adjust alpha levels in this exploratory study. Rather, we looked for three data patterns to establish consistency: 1) Statistical significance across at least two of the three genetic models on the same measure; 2) Statistical significance across multiple measures within 1 of 5 cognitive domains (i.e., memory (BVMT, HVLT, WMS), attention control (Digit Span, Color Trails 1), executive functioning (Stroop, Color Trails 2), verbal fluency (COWA, WTAR), and perceived cognitive performance (FACT-Cog); and 3) Statistical significance across multiple cognitive domains. All three patterns were necessary to establish

consistency. Because the number of participants who were tested for cardiac phenotypes was low, any gene related to any of the 5 cardiac measures was identified with the cognizance that consistency would have to be established in future studies. Statistical significance was established at $p < 0.05$.

Results

Participant Characteristics

Among 212 BCS consented to participate in the R01 trial, 207 completed this genetic analysis. However, as expected, significant difference of genotype distribution was observed by different racial groups. Due to differential genotype distribution by race, non-White participants were excluded from the analyses, and therefore only participants who self-identified as white were included, resulting in a sample size of 151. Some participants (24.5%) received CT only, while the remainder received both CT and radiotherapy (75%). The majority (65%) of BCS were more than a year since cancer treatment. Selected demographic and clinical characteristics are described in Table 1. Among the 151 BCS included in this analysis, cardiac phenotype data were obtained from 28 BCS (Supplemental Table 1).

Genetic Analysis Results for Cognition

All SNP distributions followed Hardy-Weinberg equilibrium (Table 2). Among 12 SNPs tested, three SNPs (rs429358 in *APOE*, rs1800497 in *ANKK1*, and rs10119 in *TOMM40*)

Table 1. Selected Clinical and Demographic Characteristics of Participants (*n* = 151, White only).

Variable	Level	N = 151	%
Age at diagnosis	Mean ± SD	56 ± 10.5	
Smoking	Never	96	63.6
	Former	46	30.5
	Current	9	6.0
Education status	College	97	64.2
	No College	54	35.8
Marital status	Single, Divorced, Widowed	46	30.5
	Married	102	67.5
	Other	3	2
Employment	Employed < 32 hrs/wk	23	15.2
	Employed ≥ 32 hrs/wk	49	32.5
	Other[a]	31	20.5
	Retired	42	27.8
	Unemployed	6	4
Income	<$20,000	29	19.8
	$20,000 to < $40,000	25	17.1
	$40,000 to < $80,000	45	30.8
	$80,000 to <	47	32.2
	Missing	5	—
Time since completion Category	1 Year	52	34.4
	More than 1 Year	99	65.6
Cancer treatment Category	Chemo Alone	37	24.5

[a]"Other" responses for employment included "Student", "Disabled," "On medical leave," and a selection of "other" if no available selection fit.

Table 2. Characteristics of Candidate Single-nucleotide Polymorphisms (*n* = 151).

Gene	SNP ID	Allele	Change	Poly/HT/WT	HWE	Role
APOE	rs429358	C/T	Cys156Arg	3/30/118	0.91	Cognitive function (Koleck et al., 2014; Lengacher, Reich, et al., 2015a)
BDNF	rs6265	T/C	Val66Met	5/44/102	1.00	Cognitive impairment (Ng et al., 2016)
HTR2A	rs6313	A/G	Ser34SER	26/78/47	0.90	Cognitive function (Kurita et al., 2016)
HTR2A	rs6314	A/G	His452Asn	0/28/123	0.49	
ANKK1	rs1800497	A/G	Glu713Lys	7/45/99	0.91	Cognitive function (Lengacher, Reich, et al., 2015)
AK091365	rs1487441	G/A	none	31/81/39	0.80	Cognitive function (Davies et al., 2016; Rietveld et al., 2014)
AKAP6	rs17522122	G/T	3'UTR	39/70/42	0.82	Cognitive function (Andrews et al., 2017; Davies et al., 2015, 2016)
TOMM40	rs10119	G/A	3'UTR	8/60/83	0.89	Cognitive function (Davies et al., 2015)
BCL11A	rs7581162	T/A	Intron	28/82/41	0.71	Cognitive function (Le Hellard et al., 2017)
APBA1	rs3897757	A/G	intron	33/73/45	0.97	Cognitive function (Davies et al., 2016; Sloan et al., 2010)
CYP2D6	rs5758605	A/G	upstream	31/70/50	0.88	Cognitive function, depression (Cacabelos, 2007)
MTHER	rs1801133	C/T	Ala222Asp	19/70/62	1.00	Cognitive function (Jiang et al., 2016; Schiepers et al., 2012) Heart defect (H. L. Yang et al., 2018)
Intergenic	rs28714259	G/A	none	2/24/125	0.91	Heart failure (Linschoten et al., 2018; Schneider et al., 2017)
CHD13	rs8055236	G/A	intron	4/53/94	0.72	Heart disease (Angelakopoulou et al., 2012; Bressler et al., 2010)
CXCL12	rs1746048	C/T	none	2/30/119	1.00	Cardiovascular health (Ansari et al., 2019; Spiller et al., 2020)
CDKN2B	rs1333049	G/A	none	38/75/38	1.00	Coronary artery disease (Hu et al., 2019; Trenkwalder et al., 2019)

emerged as having the most consistent significant relationships with cognitive outcomes (Memory, Attention control, Executive Functioning, Verbal fluency, and Perceived Cognitive Performance). For both rs429358 in *APOE* and rs10119 in *TOMM40*, the same pattern emerged: Statistically significant effects were observed in multiple measures of Memory (HVLT and BVMT), Executive Functioning (Color Trails), and Verbal Fluency (COWA). Effects were observed across all three genetic models (Figures 1 and 2). For rs1800497 in *ANKK1*, statistically significant effects were observed in multiple measures Memory (HVLT and BVMT), in Attention Control (WAIS Digit Span), Executive Functioning (Stroop), and Perceived Cognitive Performance (FACT-Cog). Effects were observed across all three genetic models.

Genetic Analysis Results for Cardiac Functioning

The relationships between SNPs previously associated with cardiac phenotype and cardiac outcomes were exploratory due to the small sample assessed. Two SNPs, rs8055236 in *CDH13* and rs1801133 in *MTHER* emerged as having potential relationships. rs8055236 in *CDH13* was associated with diastolic blood pressure in one genetic model (Hetero+poly vs. wild type) (Figure 3). rs1801133 in *MTHER* was associated with heart rate in the 3-group genetic model.

Discussion

Multiple studies have identified CI after CT. However, there is limited research examining the relationship between SNP and

cognitive functioning and SNP's responsible for a substantial risk of CI. Although CI is a major problem for BCS, currently there is no effective pharmacological agent to enhance cognitive functioning in this population.

Our cognitive performance tests have been selected based on previous research on cognitive functioning in cancer patients (Booth-Jones et al., 2005; Jacobs et al., 2007) and have demonstrated reliability and validity and have published normative data for adults and the domains (Bower et al., 2006). Despite the magnitude of the decreased cognitive functioning among chemo-brain BCS, there are gaps in knowledge due to variability in results due to differences in types of assessment, particularly objective and subjective assessments, and design and co-morbidities or the cancer itself (Pullens et al., 2010). Most intervention research studies use subjective measures; however, the objective measures are more precise and identify the real domain deficits in areas of cognitive functioning, such as executive functioning, memory and verbal fluency that include extensive batteries of neuropsychological tests. Although objective tests are not disputed as vital, objective measures require extensive assessment training in the delivery in a 1:1 assessment for each person as compared to assessment by subjective measures that can be performed individually by each patient. Therefore, subjective measures may be deemed as more useful, than neuropsychological tests for research.

CI symptoms of BCS vary for each person and evidence indicates genetic variations are likely to influence frequency and intensity of the symptom (S. H. Doong et al., 2015). Recently, our team and others reported on cognitive
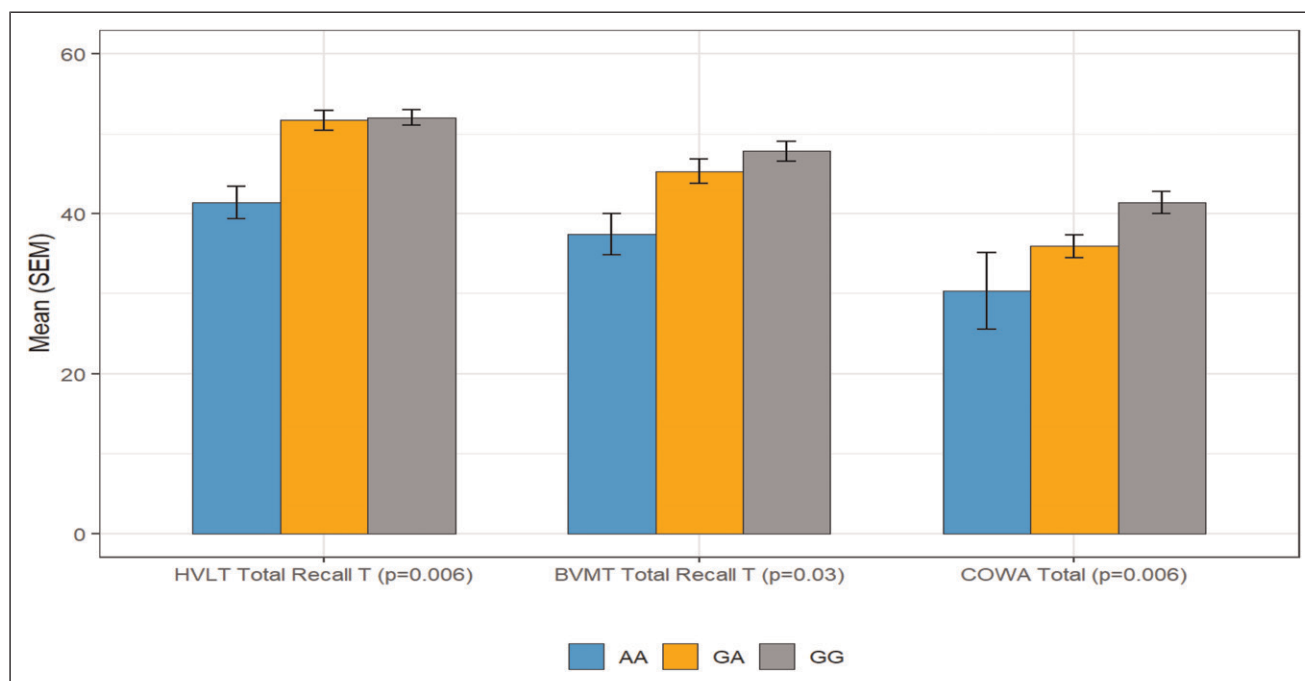
Figure 1. Cognition and rs10119 Genotype.
Note. Pattern of relationships between genotypes based on rs10119 SNP and phenotype: In rs10119 in *TOMM40*, statistically significant effects were observed in multiple measures of Memory including Executive Functioning and Verbal Fluency. Effects were observed across all three genetic models with three genotypes (AA, GA, and GG). This figure illustrates how participants that were homozygous for the A variant performed worse on these cognitive measures.
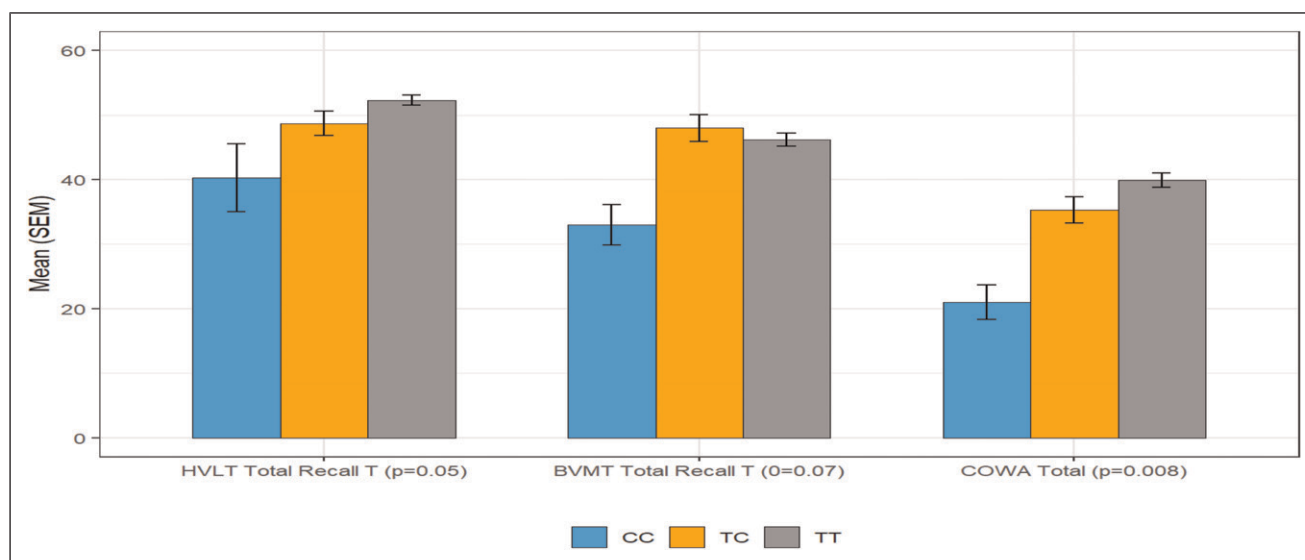

Figure 2. Cognition and rs429358 Genotype.
Note. Pattern of relationships between genotypes based on rs 429358 SNP and phenotype: In rs429358 in *APOE,* statistically significant effects were observed in multiple measures of Memory including Executive Functioning and Verbal Fluency. Effects were observed across all three genetic models with three genotypes (CC, CT, and TT). This figure illustrates how participants that were homozygous for the C variant performed worse on these cognitive measures.

functioning in BCS studies with genetic influences (Boots, E. A. et al., 2017; Gonzalez et al., 2015; Lengacher, Reich, Kip, et al., 2015). Based on our previous study (Lengacher, Reich, Kip, et al., 2015), we investigated whether genetic variations may be associated with a multitude of CI or poor cardiac

function experienced by BCS. In this study, we observed that three SNPs (rs429358 in *APOE*, rs1800497 in *ANKK1*, and rs10119 in *TOMM40*) were associated with CI.

These SNPs and genes were previously investigated by our team and others. A previous study suggested *APOE* SNP as a
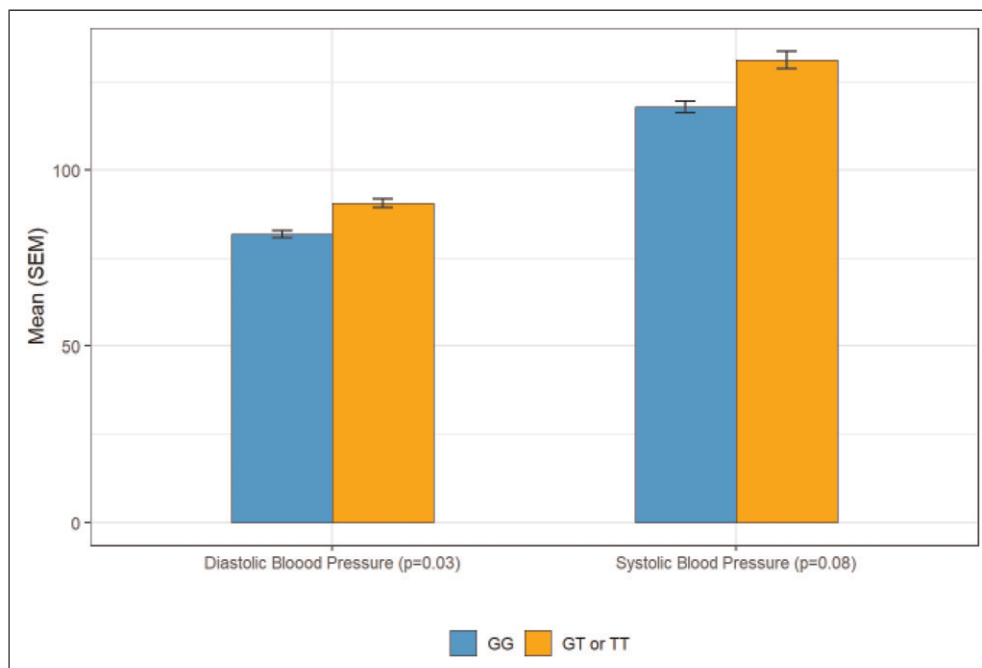
Figure 3. Blood Pressure and rs8055236 Genotype.
Note. Pattern of relationships between SNPs and phenotype: In rs8055236 in *CHD13*, a statistically significant effect was observed in diastolic blood pressure and a similar pattern (but not significant) in systolic blood pressure. This figure illustrates how participants that were homozygous for the G variant tended to have lower blood pressure.

genetic biomarker for increased vulnerability to CT-related CI (Ahles et al., 2003). Our team (Lengacher, Reich, Paterson, et al., 2015) and others previously reported that *APOE* SNP rs429358 is associated with a decline in cognitive function (Koleck et al., 2014; O'Donoghue et al., 2018; Small et al., 2011). For example, Koleck et al. (2014) performed a longitudinal study to examine the role of APOE SNP in the cognitive function of CT treated BCS (Koleck et al., 2014). They observed that changes in performance on tasks of executive function, attention, verbal learning and memory, and visual learning and memory were influenced by APOE genotype.

In this current analysis, we validated that *APOE* (rs429358) showed statistically significant association between this SNP and cognitive functioning in BCS. rs1800497 in *ANKK1* also was associated with CI in BCS. rs1800497 causes an amino acid change from Glu to Lys at codon 713, reducing D2 dopamine receptor binding and glucose metabolism in the brain (Ponce et al., 2009). Phenotypes affected by this SNP are related to CI, and our finding of an association between this SNP and CI is supported by our previous study (Lengacher, Reich, Paterson, et al., 2015) and others (Berryhill et al., 2013; Noble, 2000; Savitz et al., 2013; Spellicy et al., 2014).

TOMM40 is located at chromosome 19q13.32 and encodes the mitochondrial outer membrane complex (Gottschalk et al., 2014). With, a GWAS study on longitudinal cognitive ability data reported that SNPs in *TOMM40* were significantly associated with age-related cognitive decline (Davies et al., 2014).

In addition, SNPs in regulatory region of *TOMM40* influenced functional effect, suggesting that *TOMM40* may be associated with CI (Davies et al., 2014; Lin et al., 2017). Currently, a role of SNPs in *TOMM40* among BCS with chemo-treatment was not investigated in CI. Our results suggested that genetic variations in *TOMM40* may be related to CI among BCS.

CT-induced cardiac dysfunction is a serious and common side effect of treatment (Norton et al., 2020). Around 30% of patients develop heart failure or mild left ventricular dysfunction within 6 months among CT-treated patients and these cardiac events occur more often in patients with 65 years or older (Necela et al., 2017). However, individual variation of CT-induced cardiac dysfunction cannot be explained by known clinical risk factors. We hypothesized that genetic variants may provide better explanation. We conducted a systematic literature search to identify genetic risk factors for CT-induced cardiac dysfunction. When testing the relationships between 5 SNPs and cardiac outcomes, two SNPs, rs8055236 in *CDH13* and rs*1801133* in *MTHER* emerged as having a significant relationship with cardiac phenotype in one genetic model.

Cadherin-13 (*CDH13*) was known the important role in human diseases such as cancer, and cardiovascular disease. High expression of *CDH13* was reported in diseased vascular endothelial during atherosclerosis (Takeuchi et al., 2007). Previous studies reported that SNPs in *CDH13* associated with coronary artery disease (Burton et al., 2007; Chotchaeva et al., 2016; Samani et al., 2007). In addition, *CDH13* was identified

as one of the risk loci for CAD in a meta-analysis (van der Harst & Verweij, 2018). However, the biological function of *CDH13* on the cardiovascular system has not been established yet, especially in BCS. In previous genome-wide association studies for coronary heart disease (CHD) with 25,000 subjects and 5794 CHD events,, rs8055236 SNP in *CDH13* was associated with CHD risk (Angelakopoulou et al., 2012; Baudhuin, 2009; Bressler et al., 2010; Yan et al., 2009). Our results are consistent with results from previous studies.

Methylenetetrahydrofolate reductase (*MTHFR*) rs1801133 leads to reduced enzyme activity and causes extracellular matrix remodeling (Wang et al., 2006). This SNP was significantly associated with the risk of obstructive heart defects in previous studies (Weiner et al., 2012; Yin et al., 2012). Further, a meta-analysis of 7697 cases and 13,125 controls reported that *MTHFR* rs1801133 was associated with risk of congenital heart defects (OR. 1.25, 95% CI: 1.03–1.51) (Mamasoula et al., 2013). The T allele of the *MTHFR* rs1801133 is associated with reduced activity of *MTHFR* (Castro et al., 2004) and increased plasma homocysteine level (DeVos et al., 2008). Our results are consistent with a significant association between polymorphisms in *MTHFR* gene and increased risk of cardiac dysfunction among CT-treated BCS. There are several strengths and limitations of this analysis. The first strength is that objective neuropsychological assessments were used to test objective measures of cognitive functioning, as well as self-reports subjective measures for each participant. As a limitation, first, the biological function of the SNPs identified were not fully established. The impact of SNPs in expression or activity of genes needs to be investigated to assess potential mechanisms. Second, the sample size of this study, especially for cardiac function was small. Therefore, this sub-analysis lacked sufficient power for broad generalization. Third, non-white patients were excluded for statistical analysis. Therefore, these results may not be applied in non-white patients. Fourth we used vital signs as a cardiac outcome. Other cardiac outcomes could be further assessed for their association in the analysis. Finally, results from cardiac functioning analysis were significant only in one genetic model. Therefore, these results presented may be exploratory. This study supports an initial step supporting goals of personalized medicine to tailor symptom-relief interventions based on genetic profiles of BCS. These genetic findings may be used in the future to assist health care providers, nurses, and physicians to identifying women with breast cancer most at risk for cognitive decline and cardiac dysfunction.

In summary, we reported significant associations between genetic variations and CT-induced CI or cardiac function in BCS. These results suggest that the heterogeneity in CI and cardiac function may be influenced by genetic profiles in genes involved in cognitive function or cardiac phenotype in BCS. Further, these preliminary results provide initial targets to further examine whether BCS with specific genetic profiles may preferentially benefit from interventions designed to improve cognitive and cardiac functioning following CT.

Ethics, Knowledge Dissemination, and Impact of Study

This translational research used neuropsychological, genetic, and cognitive impairment (CI). If CI is influenced by genetic profiles, these aspects may impact medical costs of cancer care. Genetic profile identification has the potential to facilitate the development of personalized medicine pathways for optimal treatment response. Evidence may provide for broader dissemination of the intervention as a non-pharmacological treatment in cancer centers among CT-induced CI among BCS.

Data Accessibility Statement

Data will be made available to faculty researchers at Universities in the United States through a data sharing agreement and to approved members of the scientific community 3 years after the final grant completion date. This dissemination plan will undergo yearly review. Pending results, effective intervention materials and programs will be shared through a Web site or national repository.

Ethics Declarations

This study protocol was approved by the Institutional Review Board at the University of South Florida to ensure the ethical treatment of participants.

Dissemination

This reported analysis as part of a larger clinical trial, may provide for ideal delivery and broader dissemination of potential interventions based on genetic profile as a non-pharmacological treatment in cancer

centers and settings of CT-induced CI among BCS. Results of this study will be disseminated via peer-reviewed publications, scientific meetings, and oncology conferences.

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Supplemental Material

Supplemental material for this article is available online.

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