Palpitations in Women With Breast Cancer Are Associated With Polymorphisms for Neurotransmitter Genes

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OBJECTIVES: To evaluate for associations between the occurrence of palpitations reported by women prior to breast cancer surgery and single nucleotide polymorphisms (SNPs) for neurotransmitter genes.

SAMPLE & SETTING: A total of 398 women, who were scheduled for unilateral breast cancer surgery, provided detailed information on demographic and clinical characteristics and the occurrence of palpitations prior to breast cancer surgery.

METHODS & VARIABLES: The occurrence of palpitations was assessed using a single item (i.e., "heart races/pounds" in the past week ["yes"/"no"]). Blood samples were collected for genomic analyses. Multiple logistic regression analyses were used to identify associations between the occurrence of palpitations and variations in neurotransmitter genes.

RESULTS: Nine SNPs and two haplotypes among 11 candidate genes were associated with the occurrence of palpitations. These genes encode for a number of neurotransmitters and/or their receptors, including serotonin, norepinephrine, dopamine, gamma-amino butyric acid, Substance P, and neurokinin.

IMPLICATIONS FOR NURSING: These findings suggest that alterations in a variety of neurotransmitters contribute to the development of this symptom.

KEYWORDS breast cancer; cardioception; neurotransmission; palpitations; polymorphisms

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Compared to the general population, survivors of cancer have a 3.93-fold increased risk of mortality from cardiovascular disease in the first year following their cancer diagnosis (Sturgeon et al., 2019). Palpitations are a common symptom in patients with cardiovascular disease (Essa & Lip, 2021; Mayou et al., 2003). In both the general population and menopausal women, occurrence rates for palpitations range from 8% to 74% (Carpenter, Sheng, et al., 2021; Enomoto et al., 2021; Lok & Lau, 1996). In patients with breast cancer, palpitation rates range from 15% prior to surgery (Sheng, Carpenter, Paul, Cooper, et al., 2023) to between 18% and 48% at 12–24 months following oral endocrine therapy (Choo et al., 2019; Kyvernitakis et al., 2014). Palpitations in patients with cancer are associated with a higher symptom burden and significant decrements in quality of life (Sheng, Carpenter, Paul, Conley, et al., 2023; Sheng, Carpenter, Paul, Cooper, et al., 2023).

Although palpitations are a common symptom, less is known about their underlying mechanism(s). As noted in several reviews (Ala et al., 2019; Bansal et al., 2019; Essa et al., 2021; Essa & Lip, 2021), patients with cancer may experience palpitations associated with cardiac arrhythmias (e.g., atrial fibrillation, sinus tachycardia); anxiety disorders (e.g., panic attacks); a variety of miscellaneous causes (e.g., caffeine, alcohol, thyroid disorders, electrolyte imbalances); and cancer-specific causes (e.g., chemotherapy).

In the authors' previous study of patients with breast cancer (Sheng, Carpenter, Smith, et al., 2023), the occurrence of palpitations was associated with polymorphisms for interleukin (IL)-1 beta (*IL1*β), *IL10*, and *IL13*. These findings suggest that inflammatory mechanisms contribute to the occurrence

of palpitations. However, given the evidence that suggests that a variety of compounds involved in neurotransmission (e.g., catechol-O-methyltransferase [COMT] [Bastos et al., 2017], neuropeptide Y [NPY] [Shah et al., 2009]) play critical roles in cardiovascular and metabolic diseases, an equally plausible hypothesis is that their dysregulation contributes to the occurrence of palpitations. For example, reductions in COMT activity enhance the serum and tissue levels of estradiol that promote catechol estrogen accumulation and associated increases in cardiovascular disease (Bastos et al., 2017). In addition, a number of single nucleotide polymorphisms (SNPs) for *NPY* were associated with a family history and early onset of cardiovascular disease (Shah et al., 2009).

Of note, as early as 1993 (Barsky et al., 1993), the concept of cardioception (i.e., physiologic sensation of one's own heartbeat) was used to explain the lack of a one-to-one relationship between palpitations and objective changes in cardiac rhythm. As noted by Kandiah et al. (2022), a number of lines of evidence suggest that the brain may be the primary originator of palpitations in the absence of cardiac arrythmias. Specific brain regions involved in the detection of one's heartbeat (an interoceptive process) include the insula, the cingulate cortex, and a number of subcortical regions (Seeley et al., 2007). In addition, recent evidence suggests that the parasubthalamic nucleus (PSTN) is a highly interconnected node within the network of brain regions that sense and regulate autonomic functions and homeostasis (e.g., cardiac function). This network is regulated by a number of neurotransmitters, including glutamine and Substance P (Shah et al., 2022). Given the evidence that alterations in neurotransmission may be a potential mechanism for palpitations, the purpose of this study was to evaluate for associations between the occurrence of palpitations reported by women prior to breast cancer surgery and SNPs for a variety of neurotransmitter genes.

Methods

Patients and Settings

The theory of symptom management was the conceptual framework for the parent study. For this analysis, the symptom (i.e., palpitations) and person (i.e., demographic, clinical, and biologic characteristics) concepts were evaluated (Weiss et al., 2023).

This analysis draws its data from a longitudinal study that evaluated neuropathic pain and lymphedema in women following breast cancer surgery and whose details are reported elsewhere (McCann et al., 2012; Miaskowski et al., 2012). Women were recruited from breast care centers located in a comprehensive cancer center, two public hospitals, and four community practices. Women were included if they were aged 18 years or older; were scheduled for unilateral breast cancer surgery; were able to read, write, and speak English; and provided written informed consent. Exclusion criteria were as follows: scheduled for bilateral breast cancer surgery or had distant metastasis at the time of diagnosis. A total of 516 patients were approached, 410 were enrolled (response rate = 79.5%), 398 completed the enrollment assessment, and 310 provided a blood sample for genetic analysis. Commonly cited reasons for refusal to participate were too busy, overwhelmed with the cancer diagnosis, or insufficient time to complete the enrollment assessment prior to surgery.

The study was approved by the Committee on Human Research at the University of California, San Francisco, and the institutional review boards at each of the study sites. During the patient's preoperative visit, a clinician explained the study to the patient and determined their willingness to participate. For women who were willing to participate, the clinician introduced the patient to the research nurse who determined eligibility and obtained written informed consent. Then, patients completed the enrollment questionnaire and provided a blood sample an average of four days prior to surgery.

Instruments

Patients completed self-report questionnaires that provided information on demographic and clinical characteristics (e.g., age, self-reported race and ethnicity). Comorbidity burden was assessed using the Self-Administered Comorbidity Questionnaire (Brunner et al., 2008; Sangha et al., 2003). Functional status was evaluated using the Karnofsky Performance Status Scale (Karnofsky et al., 1948). Medical records were reviewed for disease and treatment information.

Occurrence of palpitations was assessed using a single item from the Menopausal Symptoms Scale, which was modified from the Seattle Midlife Women's Health Study questionnaire (Woods et al., 1999). Women were asked to indicate if they felt their "heart races/pounds" in the past week. This single-item self-report measure is comparable to the way palpitations were measured in previous studies of women with breast cancer (Choo et al., 2019; Kyvernitakis et al., 2014) and in more than 100 studies of women without (Sheng et al., 2021) breast cancer.

Candidate Gene Selection and Genotyping

Blood collection and genotyping: Genomic DNA was extracted from peripheral blood mononuclear cells using the Puregene® DNA Isolation System. Samples were genotyped using the GoldenGate® genotyping platform and processed according to a standard protocol using GenomeStudio Software.

SNP selection: A combination of tagging SNPs and literature-driven SNPs was selected for analysis. Tagging SNPs were required to be common (defined as having a minor allele frequency of 0.05 or greater) in public databases. To ensure robust genetic association analyses, quality control filtering of SNPs was performed. SNPs with call rates of less than 95% or a Hardy–Weinberg p value of less than 0.001 were excluded.

As shown in Supplementary Table 1 online, a total of 248 SNPs among 30 candidate genes passed all of the quality control filters and were included in the candidate gene analyses. The 30 candidate genes in this study are involved in various aspects of neurotransmission, drug metabolism, or transport of molecules across cell membranes. Genes involved in serotonergic neurotransmission included the following: 5-hydroxytryptamine receptor 1A (*HTR1A*), *HTR1B*, *HTR2A*, and *HTR3A*; prodynorphin (*PDYN*); tyrosine hydroxylase (*TH*); and tryptophan hydroxylase 2 (*TPH2*). Genes involved in catecholaminergic neurotransmission included solute-like carrier (SLC) family 6 member 2–noradrenaline transporter (*SLC6A2*), SLC family 6 member 3–dopamine transporter (*SLC6A3*), *COMT*, cytochrome P450 family 3 subfamily A member 4 (*CYP3A4*), galanin and GMAP prepropeptide (*GAL*), galanin receptor 1 (*GALR1*), *GALR2*, and GTP cyclohydrolase 1 (*GCH1*). Genes involved in molecular transport and drug metabolism were as follows: ATP-binding cassette subfamily B (*MDR/TAP*) member 1 (*ABCB1*), adrenoceptor alpha 1D (*ADRA1D*), *ADRA2A*, adrenoceptor beta 2 (*ADRB2*), *ADRB3*, and G protein–coupled receptor kinase 3 (*GRK3*). A number of genes involved in additional aspects of neurotransmission that were evaluated included the following: SLC family 6 member 1–GABA transporter (*SLC6A1*), SLC family 6 member 4–serotonin transporter (*SLC6A4*), nitric oxide synthase 1 (*NOS1*), nitric oxide synthase 2A (*NOS2A*), tachykinin precursor 1 (*TAC1*), tachykinin receptor 1 (*TACR1*), *NPY*, *NPY* receptor 1 (*NPY1R*), and brain-derived neurotrophic factor (*BDNF*).

All genes were identified according to the approved symbol stored in the Human Genome Organization Gene Nomenclature Committee database (www.genenames.org). Function of the genes was determined using GeneCards (Safran et al., 2021; Stelzer et al., 2016). Localization of SNPs and regional annotations were identified using the University of California, Santa Cruz, Genomics Institute's Genome Browser for the human reference assembly GRCh38/hg38 (http://genome.ucsc.edu). Potential regulatory involvement of SNPs was investigated using SNPinfo (Xu & Taylor, 2009). Potential functional roles for SNPs were investigated using annotation data from the Encyclopedia of DNA Elements (ENCODE Project Consortium, 2012) and expression quantitative trait loci (eQTL) data from the Genome-Tissue Expression Portal (GTEx Consortium, 2013). Linkage disequilibrium (LD) with other SNPs and/or eQTLs were evaluated using data from the 1000 Genomes Project with LDlink (Machiela & Chanock, 2015).

Statistical Analyses for Genetic Data

Allele and genotype frequencies were determined by gene counting. Hardy–Weinberg equilibrium was assessed using chi-square or Fisher's exact tests. For the haplotype determinations, measures of LD (i.e., D' and r^2) were computed from the patients' genotypes using Haploview, version 4.2. LD-based haplotype block definition was based on D' confidence interval (Gabriel et al., 2002). For SNPs that were members of the same haploblock, haplotypes were constructed using PHASE, version 2.1 (Stephens et al., 2001). Ancestry informative markers were used to minimize confounding because of population stratification (Halder et al., 2008).

For association tests, the following three genetic models were assessed for each SNP: additive, dominant, and recessive using chi-square or Fisher's exact tests. For the significant SNPs, the genetic model that best fit the data, by maximizing the significance of the p value, was selected for the multivariate analysis. Differences in demographic and clinical characteristics between the patients with and without palpitations were evaluated using parametric and nonparametric tests. Logistic regression analyses, which controlled for significant covariates as well as genomic estimates of and self-reported race and ethnicity, were used to evaluate for associations between SNPs and haplotypes that were significant in the bivariate analyses and membership in the palpitations group. A backwards stepwise approach was used to create the most parsimonious model. Except for genomic estimates of and self-reported race and ethnicity, only predictors with a p value of less than 0.05 were retained in the final model. Genetic model

TABLE 1. Summary of SNPs Analyzed for Neurotransmitter Genes That Demonstrated Significant Bivariate Associations With the Occurrence of Palpitations Prior to Breast Cancer Surgery

Gene	SNP	Position	Chr	MAF	Alleles	χ^2	p	Model
Serotonergic neurotransmission								
Receptors								
5-hydroxytryptamine receptor 1A								
HTR1A	rs6449693	63256017	5	0.437	A > G	FE	0.032	D
Synthesis								
Tryptophan hydroxylase 2								
TPH2	rs7955501	72350025	12	0.357	A > T	FE	0.006	D
TPH2	rs1487275	72410291	12	0.259	T > G	FE	0.028	D
Catecholaminergic neurotransmission								
Solute-like carrier family 6 member 2–noradrenaline transporter								
SLC6A2	rs17841327	55694252	16	0.321	C > A	FE	0.017	D
SLC6A2	HapA01	–	–	–	–	7.613	0.022	–
Solute-like carrier family 6 member 3–dopamine transporter								
SLC6A3	rs3863145	1392710	5	0.219	C > T	FE	0.033	D
SLC6A3	rs37022	1415628	5	0.216	T > A	FE	0.032	R
SLC6A3	rs464049	1423904	5	0.465	T > C	FE	0.043	R
Metabolism								
Catechol-O-methyltransferase								
COMT	rs4646312	19948336	22	0.371	T > C	FE	0.038	D
GTP cyclohydrolase 1								
GCH1	rs841	55310491	14	0.236	C > T	6.157	0.046	A
GCH1	rs752688	55311568	14	0.236	C > T	6.157	0.046	A
GCH1	rs12587434	55325582	14	0.236	T > G	8.452	0.015	A
GCH1	rs9671371	55328634	14	0.337	C > T	7.625	0.022	A
GCH1	rs17128050	55343878	14	0.148	T > C	FE	0.023	D
GCH1	HapA05	–	–	–	–	6.021	0.049	–
GCH1	HapB03	–	–	–	–	11.757	0.003	–
Drug metabolism								
ATP-binding cassette subfamily B (*MDR/TAP*) member 1								
ABCB1	rs2235048	87138510	7	0.471	T > C	FE	0.013	R
ABCB1	rs13233308	87244959	7	0.438	C > T	FE	0.02	D
ABCB1	HapB01	–	–	–	–	6.227	0.044	–
ABCB1	HapB02	–	–	–	–	6.39	0.041	–
Various aspects of neurotransmission								
Transporter								
Solute-like carrier family 6 member 1–GABA transporter								
SLC6A1	rs2601126	11036623	3	0.407	C > T	FE	0.009	D
SLC6A1	HapA01	–	–	–	–	8.75	0.013	–

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TABLE 1. Summary of SNPs Analyzed for Neurotransmitter Genes That Demonstrated Significant Bivariate Associations With the Occurrence of Palpitations Prior to Breast Cancer Surgery *(Continued)*

Gene	SNP	Position	Chr	MAF	Alleles	χ^2	p	Model
Various aspects of neurotransmission *(continued)*								
Nitric oxide synthase 1								
NOS1	rs3782212	117755401	12	0.27	C > T	7.098	0.029	A
Tachykinin precursor 1								
TAC1	rs7793277	97359584	7	0.267	C > G	FE	0.034	R
TAC1	rs2072100	97361783	7	0.476	A > G	FE	0.006	D
TAC1	rs1229434	97365841	7	0.429	A > G	FE	0.007	D
TAC1	HapA01	–	–	–	–	7.106	0.029	–
Tachykinin receptor 1								
TACR1	rs2111378	75354603	2	0.315	C > T	12.886	0.002	A
TACR1	rs741418	75363185	2	0.44	A > G	13.752	0.001	A
TACR1	rs9808455	75369568	2	0.479	T > C	14.279	0.001	A
TACR1	rs759588	75384548	2	0.378	C > T	6.247	0.044	A
TACR1	HapB01	–	–	–	–	12.886	0.002	–
TACR1	HapB02	–	–	–	–	9.879	0.007	–
TACR1	HapC01	–	–	–	–	13.37	0.001	–
TACR1	HapC04	–	–	–	–	14.808	0.001	–
TACR1	HapD05	–	–	–	–	6.247	0.044	–
Neuropeptide Y								
NPY	rs16148	24322337	7	0.424	T > C	FE	0.008	R
NPY	rs16478	24324607	7	0.29	C > T	FE	0.032	R

A—additive model; *ABCB*—ATP-binding cassette subfamily B (*MDR/TAP*) member 1; chr—chromosome; *COMT*—catechol-O-methyltransferase; D—dominant model; FE—Fisher's exact test; GABA—gamma-aminobutyric acid; *GCH1*—GTP cyclohydrolase 1; hap—haplotype; *HTR1A*—5-hydroxytryptamine receptor 1A, G protein coupled; MAF—minor allele frequency; *NOS1*—nitric oxide synthase 1; *NPY*—neuropeptide Y; R—recessive model; *SLC6A1*—solute-like carrier family 6 member 1–GABA transporter; *SLC6A2*—solute-like carrier family 6 member 2–noradrenaline transporter; *SLC6A3*—solute-like carrier family 6 member 3–dopamine transporter; SNP—single nucleotide polymorphism; *TAC1*—tachykinin, precursor 1; *TACR1*—tachykinin receptor 1; *TPH2*—tryptophan hydroxylase 2

fit and both unadjusted and covariate-adjusted odds ratios were estimated using Stata, version 15.0.

Results

Demographic and Clinical Characteristics

A detailed description of the differences in demographic and clinical characteristics between patients with and without palpitations is reported elsewhere (Sheng, Carpenter, Paul, Cooper, et al., 2023). Briefly, the characteristics associated with the occurrence of palpitations were lower annual household income, lower functional status, higher comorbidity burden, and an increased likelihood of self-reporting back pain.

Candidate Gene Analyses

In the bivariate analyses, 26 SNPs and 12 haplotypes in 12 genes were associated with the occurrence of palpitations (see Table 1). These genes are involved in serotonergic and catecholaminergic neurotransmission, drug metabolism, and additional aspects of neurotransmission (e.g., GABAergic mechanisms).

Regression Analyses

To better estimate the magnitude (i.e., odds ratio) and precision (i.e., confidence interval) of genotype on the odds of reporting palpitations prior to breast cancer surgery, multivariate logistic regression models were fit. Using the backward stepwise approach, only Karnofsky Performance Status Scale scores in 10-unit increments (functional status) and the occurrence of back pain remained significant in the logistic regression model (Sheng, Carpenter, Smith, et al., 2023) and were included as covariates in subsequent models that evaluated genotypic predictors. After controlling

TABLE 2. Multiple Logistic Regression Analyses for Single Nucleotide Polymorphisms in Neurotransmitter Genes and the Occurrence of Palpitations in Women Prior to Breast Cancer Surgery

Predictor	Adj OR	SE	95% CI	Z	p
Serotonergic neurotransmitters					
HTR1A rs6449693	0.48	0.17	[0.24, 0.95]	−2.12	0.034
KPS score	0.97	0.01	[0.94, 0.99]	−2.35	0.019
Occurrence of back pain	2.02	0.74	[0.98, 4.13]	1.91	0.056
Overall model fit: $\chi^2 = 24.63$; $p = 0.0034$; pseudo $R^2 = 0.0944$					
TPH2 rs7955501	2.58	1.03	[1.18, 5.64]	2.38	0.017
KPS score	0.97	0.01	[0.94, 0.99]	−2.49	0.013
Occurrence of back pain	1.87	0.69	[0.9, 3.85]	1.69	0.092
Overall model fit: $\chi^2 = 26.25$; $p = 0.0019$; pseudo $R^2 = 0.1009$					
Catecholaminergic neurotransmitters					
SLC6A2 rs17841327	0.41	0.14	[0.21, 0.81]	−2.56	0.01
KPS score	0.97	0.01	[0.94, 0.99]	−2.28	0.023
Occurrence of back pain	2.17	0.8	[1.05, 4.47]	2.1	0.035
Overall model fit: $\chi^2 = 26.92$; $p = 0.0014$; pseudo $R^2 = 0.1032$					
SLC6A3 rs37022	4.48	3.03	[1.19, 16.87]	2.22	0.026
KPS score	0.97	0.01	[0.94, 0.99]	−2.12	0.034
Occurrence of back pain	2.13	0.78	[1.04, 4.38]	2.06	0.039
Overall model fit: $\chi^2 = 24.86$; $p = 0.0031$; pseudo $R^2 = 0.0953$					
COMT rs4646312	0.45	0.16	[0.23, 0.9]	−2.26	0.024
KPS score	0.97	0.01	[0.94, 0.99]	−2.41	0.016
Occurrence of back pain	2.3	0.85	[1.11, 4.74]	2.25	0.024
Overall model fit: $\chi^2 = 25.33$; $p = 0.0026$; pseudo $R^2 = 0.0971$					
GCH1 rs17128050	0.32	0.15	[0.13, 0.81]	−2.41	0.016
KPS score	0.97	0.01	[0.94, 0.99]	−2.26	0.024
Occurrence of back pain	2.24	0.83	[1.09, 4.62]	2.18	0.029
Overall model fit: $\chi^2 = 26.93$; $p = 0.0014$; pseudo $R^2 = 0.1032$					
Drug metabolism					
ABCB1 HapB01	0.57	0.16	[0.33, 0.99]	−1.99	0.047
KPS score	0.97	0.01	[0.94, 0.99]	−2.34	0.019
Occurrence of back pain	1.99	0.73	[0.96, 4.1]	1.86	0.063
Overall model fit: $\chi^2 = 24.84$; $p = 0.0032$; pseudo $R^2 = 0.0956$					

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TABLE 2. Multiple Logistic Regression Analyses for Single Nucleotide Polymorphisms in Neurotransmitter Genes and the Occurrence of Palpitations in Women Prior to Breast Cancer Surgery *(Continued)*

Predictor	Adj OR	SE	95% CI	Z	p
Various aspects of neurotransmission					
SLC6A1 rs2601126	3	1.27	[1.31, 6.89]	2.59	0.01
KPS score	0.97	0.01	[0.94, 0.99]	–2.23	0.026
Occurrence of back pain	2.03	0.75	[0.99, 4.18]	1.92	0.055
Overall model fit: $\chi^2 = 27.96$; p = 0.001; pseudo $R^2 = 0.1072$					
TAC1 rs1229434	2.74	1.22	[1.14, 6.57]	2.26	0.024
KPS score	0.97	0.01	[0.94, 0.99]	–2.25	0.025
Occurrence of back pain	1.9	0.7	[0.92, 3.92]	1.75	0.081
Overall model fit: $\chi^2 = 26.1$; p = 0.002; pseudo $R^2 = 0.1001$					
TACR1 HapB02	1.89	0.5	[1.13, 3.16]	2.41	0.016
KPS score	0.96	0.01	[0.94, 0.99]	–2.59	0.01
Occurrence of back pain	2.25	0.83	[1.1, 4.62]	2.21	0.027
Overall model fit: $\chi^2 = 26.2$; p = 0.0019; pseudo $R^2 = 0.1005$					
NPY rs16148	3.05	1.28	[1.34, 6.94]	2.67	0.008
KPS score	0.97	0.01	[0.94, 0.99]	–2.27	0.023
Occurrence of back pain	2.28	0.86	[1.09, 4.77]	2.2	0.028
Overall model fit: $\chi^2 = 27.3$; p = 0.0012; pseudo $R^2 = 0.1052$					

ABCB1—ATP-binding cassette subfamily B (*MDR/TAP*) member 1; adj—adjusted; CI—confidence interval; *COMT*—catechol-O-methyltransferase; *GCH1*—GTP cyclohydrolase 1; hap—haplotype; *HTR1A*—5-hydroxytryptamine receptor 1A, G protein coupled; KPS—Karnofsky Performance Status Scale; *NPY*—neuropeptide Y; OR—odds ratio; SE—standard error; *SLC6A1*—solute-like carrier family 6 member 1–GABA transporter; *SLC6A2*—solute-like carrier family 6 member 2–noradrenaline transporter; *SLC6A3*—solute-like carrier family 6 member 3–dopamine transporter; *TAC1*—tachykinin precursor 1; *TACR1*—tachykinin receptor 1; *TPH2*—tryptophan hydroxylase 2

Note. This table depicts multiple logistic regression analyses of candidate gene associations with no palpitations versus palpitations. For each model, the first 3 principal components identified from the analysis of ancestry informative markers, as well as self-report race and ethnicity, were retained in all models to adjust for potential confounding due to race or ethnicity (data not shown). Predictors evaluated in each model included genotype (*HTR1A* rs6449693: AA versus AG + GG; *TPH2* rs7955501: AA versus AT + TT; *SLC6A2* rs17841327: CC versus CA + AA; *SLC6A3* rs37022: TT + TA versus AA; *COMT* rs4646312 TT versus TC + CC; *GCH1* rs17128050: TT versus TC + CC; *ABCB1* HapB01: rs9282564 and rs13233308; *SLC6A1* rs2601126: CC versus CT + TT; *TAC1* rs1229434: AA versus AG + GG; *TACR1* HapB02: rs2111378 and rs3771825; *NPY* rs16148: TT + TC versus CC), KPS score (in 10 unit increments), and self-reported occurrence of back pain.

for Karnofsky Performance Status Scale score, the occurrence of back pain, self-reported and genomic estimates of race and ethnicity, and variations in other SNPs/haplotypes within the same gene, 9 SNPs and 2 haplotypes among 11 candidate genes were associated with the occurrence of palpitations (see Table 2).

Serotonergic Neurotransmission

For *HTR1A* rs6449693, carrying one or two doses of rare allele (AA versus AG + GG) was associated with a 52% decrease in the odds of belonging to the palpitations group (see Figure 1A). For *TPH2* rs7955501, carrying one or two doses of rare allele (AA versus AT + TT) was associated with a 2.58-fold increase in the odds of belonging to the palpitations group (see Figure 1B).

Catecholaminergic Neurotransmission

For *SLC6A2* rs17841327, carrying one or two doses of rare allele (CC versus CA + AA) was associated with a 59% decrease in the odds of belonging to the

palpitations group (see Figure 2A). For *SLC6A3* rs37022, carrying two doses of rare allele (TT + TA versus AA) was associated with a 4.48-fold increase in the odds of belonging to the palpitations group (see Figure 2B). For *COMT* rs4646312, carrying one or two doses of the rare allele (TT versus TC + CC) was associated with a 55% decrease in the odds of belonging to the palpitations group (see Figure 2C). For *GCH1* rs17128050, carrying one or two doses of rare allele (TT versus TC + CC) was associated with a 68% decrease in the odds of belonging to the palpitations group (see Figure 2D).

Drug Metabolism

For *ABCB1* HapB01, each additional dose of the haplotype that consisted of rs9282564 and rs13233308 was associated with a 43% decrease in the odds of belonging to the palpitations group.

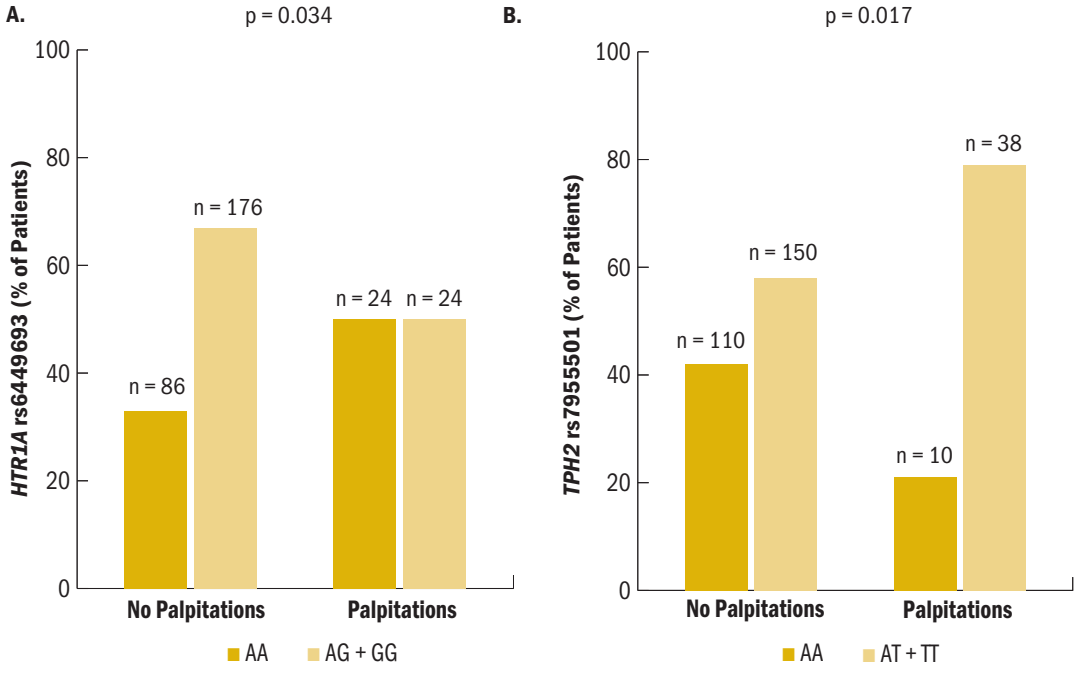
Various Aspects of Neurotransmission

For *SLC6A1* rs2601126, carrying one or two doses of rare allele (CC versus CT + TT) was associated with a threefold increase in the odds of belonging to the palpitations group (see Figure 3A). For *TAC1* rs1229434, carrying one or two doses of rare allele (AA versus AG + GG) was associated with a 2.74-fold increase in the odds of belonging to the palpitations group (see Figure 3B). For *TACR1* HapB02, each additional dose of the haplotype, which consisted of rs2111378 and rs3771825, was associated with a 1.89-fold increase in the odds of belonging to the palpitations group. For *NPY* rs16148, carrying two doses of rare allele (TT + TC versus CC) was associated with a 3.05-fold increase in the odds of belonging to the palpitations group (see Figure 3C).

Discussion

This study is the first to evaluate for associations between the occurrence of palpitations in women prior to breast cancer surgery and variations in neurotransmitter genes. These findings build on the authors' previous work that identified associations between this symptom and polymorphisms for cytokine genes (Sheng, Carpenter, Smith, et al., 2023). In line with the authors' a priori hypothesis, the results

FIGURE 1. Results for Single Nucleotide Polymorphisms Involved in Serotonergic Neurotransmission

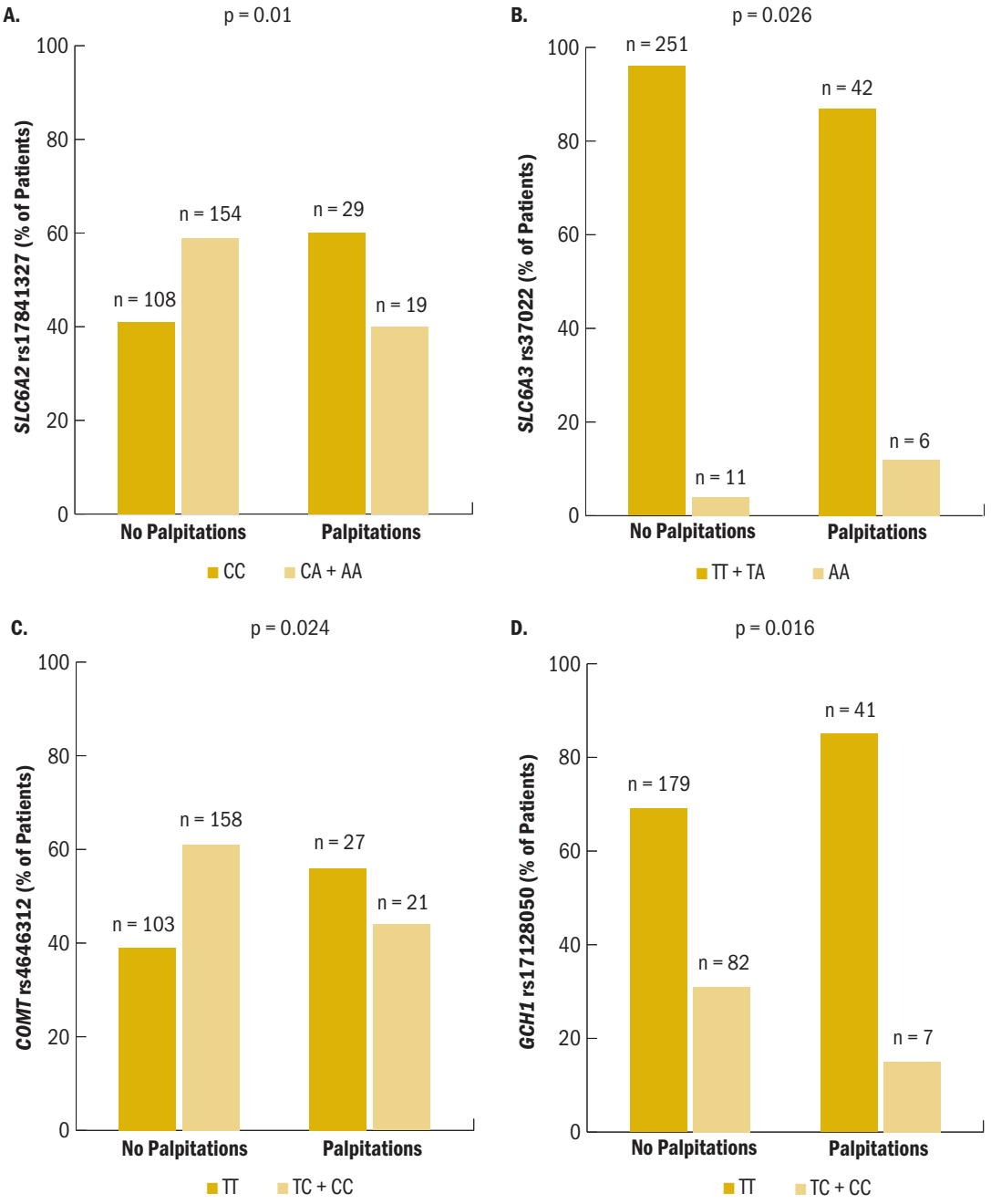


HTR1A—5-hydroxytryptamine receptor 1A; *TPH2*—tryptophan hydroxylase 2

Note. Figure A depicts differences between the palpitations groups in the percentages of patients who were homozygous for the common allele (AA) or heterozygous or homozygous for the rare allele (AG + GG) for rs6449693 in *HTR1A*.

Note. Figure B depicts differences between the palpitations groups in the percentages of patients who were homozygous for the common allele (AA) or heterozygous or homozygous for the rare allele (AA+TT) for rs7955501 in *TPH2*.

FIGURE 2. Results for Single Nucleotide Polymorphisms Involved in Catecholaminergic Neurotransmission



COMT—catechol-O-methyltransferase; *GCH1*—GTP cyclohydrolase 1; *SLC6A2*—solute-like carrier family 6 member 2–noradrenaline transporter; *SLC6A3*—solute-like carrier family 6 member 3–dopamine transporter

Note. Figure A depicts differences between the palpitations groups in the percentages of patients who were homozygous for the common allele (CC) or heterozygous or homozygous for the rare allele (CA + AA) for rs17841327 in *SLC6A2*.

Note. Figure B depicts differences between the palpitations groups in the percentages of patients who were homozygous or heterozygous for the common allele (TT + TA) or homozygous for the rare allele (AA) for rs37022 in *SLC6A3*.

Note. Figure C depicts differences between the palpitations groups in the percentages of patients who were homozygous for the common allele (TT) or heterozygous or homozygous for the rare allele (TC + CC) for rs4646312 in *COMT*.

Note. Figure D depicts differences between the palpitations groups in the percentages of patients who were homozygous for the common allele (TT) or heterozygous or homozygous for the rare allele (TC + CC) for rs17128050 in *GCH1*.

of this study suggest that serotonergic, catecholaminergic, GABAergic, and dopaminergic mechanisms are associated with the occurrence of palpitations.

Serotonergic Neurotransmission

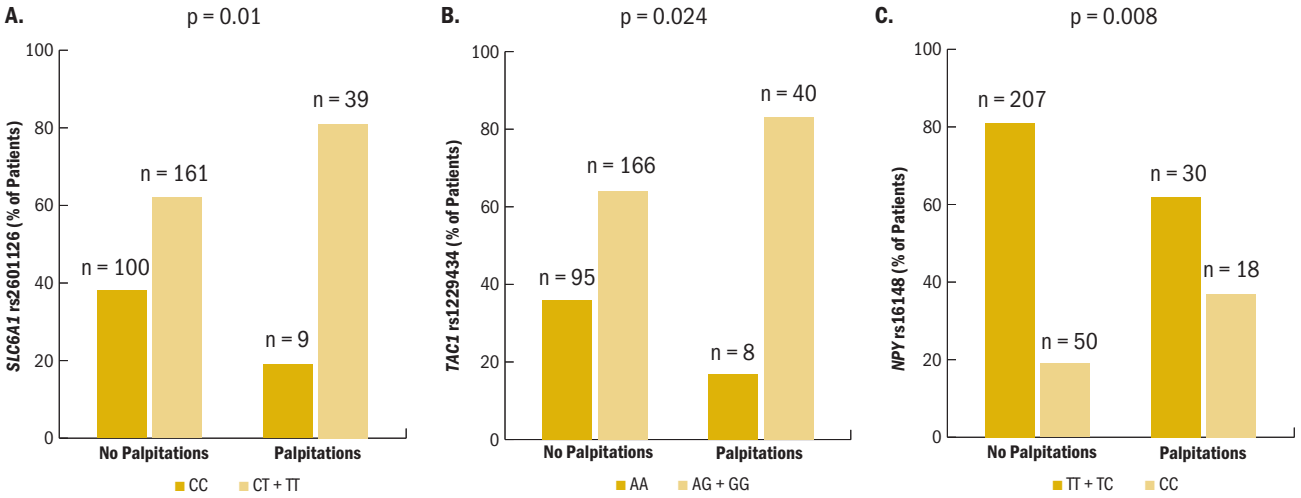
Of the seven serotonergic genes evaluated, only two SNPs in two different genes (i.e., *HTR1A* rs6449693 and *TPH2* rs7955501) remained significant in the multivariate analyses. The *HTR1A* gene encodes a G protein–coupled receptor for 5-hydroxytryptamine (i.e., serotonin). This receptor plays a role in the regulation of dopamine and serotonin levels in the brain with resultant influences on neural activity, mood, and behavior (Pucadyil et al., 2005). In terms of cardiovascular effects, dopamine stimulates both adrenoceptors and dopamine receptors with associated increases in blood pressure, tachycardia, increases in cardiac rhythmicity, and dose-dependent increases and decreases in vascular tone (Bucolo et al., 2019; Neumann et al., 2023).

TPH2 encodes for a member of the protein-dependent aromatic acid hydroxylase family that is a rate-limiting enzyme in the synthesis of serotonin in the central nervous system (Safran et al., 2021; Stelzer et al., 2016). Serotonergic neurotransmission plays a critical role in many chronic conditions, including bipolar affective disorder (Fan et al., 2021; Liu et al., 2022), major depressive disorder (Fan et al., 2021; Liu et al., 2022), and attention deficit hyperactivity disorder (Abo El Fotoh et al., 2020). Of note, in a study of *TPH2*-deficient rats, the absence of serotonin in the central nervous system resulted in a blunted response to acute stress (Brivio et al., 2018; Sbrini et al., 2020). Although both of these SNPs are intron variants with no known function, alterations in serotonin are associated with a number of anxiety and depressive disorders. Patients with these disorders report a variety of somatic symptoms, including palpitations (Liu et al., 2019). In addition, higher levels of perceived stress are associated with palpitations (Carpenter, Tisdale, et al., 2021). These findings suggest that alterations in serotonin may be involved in the occurrence of palpitations through the regulation of patients' emotional state.

Catecholaminergic Neurotransmission

Of the eight catecholaminergic genes evaluated, only four SNPs in four different genes (i.e., *SLC6A2* rs17841327, *SLC6A3* rs37022, *COMT* rs4646312, and *GCH1* rs17128050) were associated with the occurrence of palpitations. All four of these SNPs are intron variants. Variations in these genes are involved

FIGURE 3. Results for Single Nucleotide Polymorphisms Involved in Various Aspects of Neurotransmission



GABA—gamma-aminobutyric acid; *NPY*—neuropeptide Y; *SLC6A1*—solute-like carrier family 6 member 1–GABA transporter; *TAC1*—tachykinin precursor 1

Note. Figure A depicts differences between the palpitations groups in the percentages of patients who were homozygous for the common allele (CC) or heterozygous or homozygous for the rare allele (CT + TT) for rs2601126 in *SLC6A1*.

Note. Figure B depicts differences between the palpitations groups in the percentages of patients who were who were homozygous for the common allele (AA) or heterozygous or homozygous for the rare allele (AG + GG) for rs1229434 in *TAC1*.

Note. Figure C depicts differences between the palpitations groups in the percentages of patients who were homozygous or heterozygous for the common allele (TT + TC) or homozygous for the rare allele (CC) for rs16148 in *NPY*.

in the synthesis and signal transduction of catecholamines, including norepinephrine, dopamine, and epinephrine.

SLC6A2 encodes the norepinephrine transporter protein that is responsible for the removal of norepinephrine and regulation of norepinephrine levels (Safran et al., 2021; Stelzer et al., 2016). This transporter is found in mammalian hearts (Palomar et al., 2011). Norepinephrine transporter deficiency increases sympathetic activation and is associated with panic disorder (Esler et al., 2006). In addition, a mutation in *SLC6A2* was identified as a cause of orthostatic intolerance, a primary symptom of postural tachycardia (Shannon et al., 2000). Palpitations can occur in patients with panic disorders or postural tachycardia (Weinstock et al., 2021). Taken together, it is reasonable to hypothesize that changes in norepinephrine levels play a role in the occurrence of palpitations.

SLC6A3 encodes the dopamine transporter that is responsible for the active reuptake of dopamine from the extracellular space into neurons (Carvelli et al., 2008). Because this transporter is found in mammalian hearts (Palomar et al., 2011), the administration of dopamine results in an increase in heart rate (Bucolo et al., 2019; Neumann et al., 2023). Although previous studies reported on associations between polymorphisms for *SLC6A3* and schizophrenia (Xu et al., 2020), suicidal behavior (Rafikova et al., 2021), and depression (Dong et al., 2009), no studies of associations with palpitations were identified.

COMT is a key enzyme involved in the degradation of dopamine (Chen et al., 2004), epinephrine, and norepinephrine (Männistö & Kaakkola, 1999). As noted in two reviews (Bastos et al., 2017; Hall et al., 2019), COMT is involved in a number of neuropsychiatric disorders and plays a role in emotional regulation, cognition, pain perception, and addictive behavior. In addition, polymorphisms in *COMT* are associated with acute coronary events, hypertension, atherosclerosis, and an increased risk of cardiovascular disease (Almas et al., 2018; Bastos et al., 2017; Hall et al., 2019).

COMT rs4646312 may be functional as splicing quantitative trait loci (i.e., loci that regulate alternative splicing of messenger RNA [Garrido-Martín et al., 2021]) in the heart's atrial appendage, as well as in the cerebral hemispheres and the cerebellum (GTEx Consortium, 2013). The left atrial appendage is a small ear-shaped outpouching of the muscular wall of the left atrium. In patients with atrial fibrillation, this structure does not function properly, blood clots form, and patients are at increased risk for stroke (Al-Saady et al., 1999; Ueno et al., 2023). Given that patients with atrial fibrillation often report palpitations (Huang et al., 2023), COMT warrants additional investigation.

GCH1 is the rate-limiting enzyme involved in the synthesis of catecholamines and nitric oxide. In addition, this gene is responsible for the synthesis of tetrahydrobiopterin (BH4), an essential cofactor in the synthesis of hydroxylases involved in the metabolism of catecholamines (Thöny & Blau, 1997; Thöny et al., 2000). Although no associations were reported for *GCH1* rs17128050 and palpitations, variations in this gene are associated with endothelial dysfunction and oxidative stress in patients with type 2 diabetes (Wolkow et al., 2014). In addition, in a twin study (Zhang et al., 2007), baroreflex dysfunction, reduced heart rate variability, fluctuations in blood pressure, and increased minimum heart rate were associated with variations in *GCH1*. *GCH1* expression and BH4 synthesis can also be stimulated by proinflammatory cytokines (e.g., IL1β) and inhibited by anti-inflammatory cytokines (e.g., IL4, IL10) (Fanet et al., 2021). In the authors' previous study of the same sample (Sheng, Carpenter, Smith, et al., 2023), associations were found between a number of polymorphisms for *IL1β*, *IL10*, and *IL13*, and the occurrence of palpitations. Taken together, these findings suggest that additional research is warranted on the role of *GCH1* as a potential mechanism for palpitations.

Drug Metabolism

Of the six genes involved in molecular transport or drug metabolism that were evaluated, only a haplotype in *ABCB1* (that included rs9282564 and rs13233308) was associated with the occurrence of palpitations. *ABCB1* encodes P-glycoprotein 1 (P-gp), known as the multidrug resistance protein 1 in humans. P-gp plays a significant role in drug pharmacokinetics by facilitating the transport of drugs from the intracellular to the extracellular domain (Ambudkar et al., 1999; Gottesman et al., 1996). According to SNPinfo (Xu & Taylor, 2009), *ABCB1* rs9282564 is a missense variant that can act as an exon splicing enhancer or an exon splicing silencer that can affect the regulation of protein products (Kjer-Hansen & Weatheritt, 2023). Although no associations were found with palpitations, this SNP was associated with opioid addiction (Christoffersen et al., 2016), efficacy and safety of immunosuppressant therapy after heart transplantation (Sánchez-Lázaro et al., 2015), and chronic depression (Ray et al., 2015). No eQTLs were found for rs9282564. However, an evaluation

of *ABCB1* rs13233308 found that eQTLs in the atrial appendage, as well as in the cerebral hemispheres and the cerebellum, were associated with the RUN domain–containing protein 3B (*RUNDC3B*) gene. In the setting of multidrug resistance, overexpression of *ABCB1* creates an amplicon that includes the nearby gene *RUNDC3B*. As noted previously, alterations in the atrial appendage are associated with atrial fibrillation and palpitations.

Genes Involved in Various Aspects of Neurotransmission

Of the nine genes involved in various aspects of neurotransmission that were evaluated, three SNPs and one haplotype in four different genes (i.e., *SLC6A1* rs26011126, *TAC1* rs1229434, a *TACR1* haplotype [that included s2111378 and rs3771825], and *NPY* rs16148) were associated with the occurrence of palpitations. Variations in these genes contribute of a number of chronic conditions.

SLC6A1 encodes the gamma-aminobutyric acid (GABA) transporter that removes excess GABA from the synaptic cleft to maintain neurotransmitter homeostasis. Given that GABA is the predominant inhibitory neurotransmitter in the central nervous system, variations in *SLC6A1* are linked to a variety of neurodevelopmental disorders and seizures (Kahen et al., 2022; Mermer et al., 2021). Although no studies have reported on an association between *SLC6A1* rs26011126 (an intron variant) and palpitations, evidence suggests that GABA plays a role in the pathophysiology of anxiety disorders (Kalueff & Nutt, 2007; Thoeringer et al., 2009). Given the connection between palpitations and anxiety disorders (Enomoto et al., 2021; Essa & Lip, 2021), these findings suggest a potential role of *SLC6A1* in the development of palpitations.

TAC1 encodes a precursor protein called preprotachykinin-1. This protein undergoes posttranslational modification to produce Substance P and neurokinin A. These peptides are involved in the excitation of neurons, evoke behavioral responses, are potent vasodilators and secretagogues, and contract (directly or indirectly) many smooth muscles (Safran et al., 2021; Stelzer et al., 2016). *TACR1*, which encodes the receptor for Substance P, is located in both the peripheral and central nervous systems (Safran et al., 2021; Stelzer et al., 2016). As noted in the introduction to the current article, the PSTN is a highly connected node that appears to be involved in the process of interoception. Based on preclinical studies, the PSTN is characterized by a high density of cells expressing the *TAC1* gene. In addition, the PSTN is innervated by serotonergic terminals from the dorsal raphe nucleus and dopaminergic terminals from the ventral tegmental area (Shah et al., 2022). The SNPs for *TAC1* and *TACR1* in the current study are intron variants that may be in LD with functional SNPs. Given the potential importance of interoceptive processes in the perception of palpitations (Barsky, 2001; Kandiah et al., 2022), these genes warrant additional investigation.

NPY encodes a neuropeptide that is expressed throughout the central nervous system. NPY is involved in a variety of biologic processes including cortical excitability, responses to stress, food intake, circadian rhythms, and cardiovascular function (Safran et al., 2021; Stelzer et al., 2016). Although an intron variant, an association was found between *NPY* rs16148 and cervical vertigo (Han et al., 2018), a condition characterized by palpitations (Kim et al., 2019; Sharma et al., 2021). In addition, lower levels of NPY were associated with obesity in pre- and postmenopausal women, and higher levels of NPY were associated with hot flashes in postmenopausal women. Given that obesity (Powell-Wiley et al., 2021) and hot flashes (Zhu et al., 2020) are independently associated with an increased risk of cardiovascular disease and hot flashes are associated with palpitations in patients with breast cancer (Sheng, Carpenter, Paul, Cooper, et al., 2023), this gene warrants additional investigation.

Limitations

Several limitations warrant consideration. Given that only women with breast cancer were evaluated, future studies need to evaluate men and women with different types of cancer. Given the study's cross-sectional design, associations between changes in palpitations during the course of treatment for breast cancer and neurotransmitter gene polymorphisms warrant evaluation in future studies. Given the relatively small

KNOWLEDGE TRANSLATION

- A number of polymorphisms for neurotransmitter genes are associated with the occurrence of palpitations in women prior to breast cancer surgery.
- A variety of neurotransmitters (e.g., serotonin, dopamine) may play a role in palpitations in women with breast cancer.
- An increased understanding of the underlying mechanisms of palpitations may enable the identification of high-risk patients and the development and testing of novel therapeutic interventions.

sample size and the exploratory nature of this study, replication of these findings is required before any clinical implications can be inferred.

Implications for Practice and Research

Findings from the current study suggest the involvement of serotonergic, catecholaminergic, GABAergic, and dopaminergic mechanisms in the occurrence of palpitations in women prior to breast cancer surgery. These findings add to the knowledge of the potential mechanisms that underlie this symptom. These findings, as well as the authors' previous findings on associations with inflammatory genes (Sheng, Carpenter, Smith, et al., 2023), suggest that the mechanisms that underlie palpitations are complex. However, additional research is warranted to confirm or refute these findings.

Future studies need to evaluate additional neurotransmitter genes (e.g., glutamate). In addition, future studies of women with breast cancer who report palpitations can include a more in-depth evaluation of the symptom (e.g., severity, frequency, distress); an examination of additional clinical characteristics (e.g., history or co-occurrence of cardiovascular disease, use of relevant medications); and an evaluation of a variety of biomarkers (e.g., gene expression, DNA methylation), as well as measures of interoceptive accuracy (Desmedt et al., 2023). This multifaceted approach will enable the elucidation of the underlying mechanisms for palpitations. An increased understanding of these mechanisms may enable the identification of high-risk patients and the development and testing of novel interventions for this significant symptom.

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