Self-Reported Cancer-Related Cognitive Impairment in Patients With Breast Cancer Is Associated With Potassium Channel Gene Polymorphisms

Kate R. Oppegaard, RN, PhD, OCN®, Marilyn J. Hammer, PhD, DC, RN, FAAN, Yvette P. Conley, PhD, FAAN, Carolyn S. Harris, PhD, RN, BMTCN®, OCN®, Bruce A. Cooper, PhD, Steven M. Paul, PhD, Joosun Shin, PhD, RN, OCN®, Lisa Morse, MS, RN, CNS, Gary M. Abrams, MD, Jon D. Levine, PhD, MD, and Christine Miaskowski, PhD, RN

OBJECTIVES: To evaluate for associations of polymorphisms for potassium channel genes in patients with breast cancer who were classified as having high or low–moderate levels of cancer-related cognitive impairment (CRCI).

SAMPLE & SETTING: 397 women who were scheduled to undergo surgery for breast cancer on one breast were recruited from breast care centers located in a comprehensive cancer center, two public hospitals, and four community practices.

METHODS & VARIABLES: CRCI was assessed using the Attentional Function Index prior to and for six months after surgery. The attentional function classes were identified using growth mixture modeling.

RESULTS: Differences between patients in the high versus low–moderate attentional function classes were evaluated. Six single nucleotide polymorphisms for potassium channel genes were associated with low–moderate class membership.

IMPLICATIONS FOR NURSING: The results contribute to knowledge of the mechanisms for CRCI. These findings may lead to the identification of high-risk patients and the development of novel therapeutics.

KEYWORDS attentional function; breast cancer; cancer-related cognitive impairment

***ONF, 51*(3), 263–274.**

DOI 10.1188/24.ONF.263-274

Cancer-related cognitive impairment (CRCI) is reported by 57% of patients with breast cancer (Schmidt et al., 2016). CRCI can include difficulties with attention and concentration, decrements in motivation, an inability to recall names of familiar objects or people, and memory loss (Mayo et al., 2021). The molecular mechanisms that underlie CRCI are complex and not fully understood (Oppegaard et al., 2022). Therefore, progress in the development of prevention and mitigation strategies remains limited (Onzi et al., 2022).

As noted in a previously published scoping review (Oppegaard et al., 2022), limited information is available on associations between CRCI and a variety of molecular markers. Inflammatory biomarkers (e.g., circulating cytokines, inflammatory genes) have been the most frequently studied. This line of inquiry is logical because cancer can induce inflammatory processes through multiple pathways, including tumor-related factors (Singh et al., 2019), psychological stress (Han et al., 2016), and as a consequence of treatment(s) (Bagnall-Moreau et al., 2019). Given that inflammation occurs in response to and/or in concert with other biologic processes (Medzhitov, 2008), an evaluation of additional molecular mechanisms may provide new insights into the causes of CRCI.

Although not studied in relationship to CRCI, potassium channels are ion channels that are distributed throughout the central nervous system (e.g., frontal cortex, basal ganglia) (Alam et al., 2023). Evidence suggests that potassium channels are important mediators of inflammation (Di et al.,

2018). For example, in response to inflammation, potassium channels located in brain endothelial cells increase the permeability of the blood–brain barrier and contribute to neuroinflammation (Bittner et al., 2014). Equally important, stress-induced inflammatory signaling triggers the opening of potassium channels, which leads to a reduction in neuronal firing and decrements in cognitive function (Arnsten et al., 2023). Given that potassium channel genes have the potential to serve as therapeutic targets (Humphries & Dart, 2015), an evaluation of associations between CRCI and potassium channel genes is warranted.

In the authors' previous study of patients with breast cancer who were assessed prior to and for six months after surgery (i.e., seven assessments) (Merriman et al., 2014), self-reported CRCI was evaluated using the Attentional Function Index (AFI) (Cimprich et al., 2011). Using growth mixture modeling, the following three distinct attentional function profiles were identified: high (N = 165), moderate (N = 101), and low–moderate (N = 131). Because no previous studies have evaluated for associations between CRCI and potassium channel genes in patients with breast cancer, the purpose of this study, which used the profiles identified in the previous growth mixture modeling analysis (Merriman et al., 2014), was to evaluate for associations between the phenotypic extremes (i.e., the high class versus the low–moderate class) and polymorphisms for potassium channel genes.

Methods

Sample and Setting

The theoretical framework for the overall study was the theory of symptom management (Weiss et al., 2023). For the current analysis, symptom (i.e., CRCI) and person (i.e., demographic, clinical, and biologic characteristics) concepts were evaluated.

Patients were recruited from breast care centers located in a comprehensive cancer center, two public hospitals, and four community practices. Patients were eligible to participate if they were aged 18 years or older; were scheduled to undergo surgery on one breast; were able to read, write, and understand English; and gave written informed consent. Patients with distant metastases at the time of diagnosis were excluded. Of the 516 patients who were approached, 410 enrolled in the study (80% response rate), and 397 patients completed the enrollment assessment. The most common reasons for refusal were being too busy or feeling overwhelmed.

The study was approved by the Committee on Human Research at the University of California, San Francisco, and by the institutional review boards at each of the study sites. During preoperative visits, a clinical staff member explained the study and invited patients to participate. Women who were willing to participate were introduced to a research nurse, who determined eligibility. After providing written informed consent, patients completed baseline questionnaires and had a blood sample drawn a mean of four days prior to surgery. Follow-up questionnaires were completed each month for six months after surgery (i.e., seven assessments during a six-month period). Medical records were reviewed for disease and treatment information.

Measures

Patients completed a demographic questionnaire that obtained information on age, gender, ethnicity, marital status, living arrangements, education, employment status, and income. In addition, patients rated their functional status using the Karnofsky Performance Status Scale, with scores ranging from 30 ("I feel severely disabled and need to be hospitalized") to 100 ("I feel normal; I have no complaints or symptoms") (Karnofsky, 1977). To evaluate multimorbidity, patients completed the Self-Administered Comorbidity Questionnaire. The Self-Administered Comorbidity Questionnaire consists of 13 common medical conditions simplified into language that can be understood without prior medical knowledge. Patients indicated whether they had the condition, if they received treatment for it (proxy for disease severity), and if it limited their activities (indication of functional limitations). For each condition, the patient can receive a maximum of three points. Total scores on the Self-Administered Comorbidity Questionnaire range from 0 to 39, with higher scores indicating a greater comorbidity burden (Sangha et al., 2003).

Self-reported CRCI was assessed using the AFI (Cimprich et al., 2011). The AFI consists of 13 items designed to measure perceived effectiveness in daily activities supported by attention and working memory. Higher mean scores on a numeric rating scale ranging from 0 to 10 indicate greater capacity to direct attention. Scores are grouped into categories of attentional function (i.e., a score less than 5 indicates low function, scores of 5–7.5 indicate moderate function, and scores greater than 7.5 indicate high function). Its Cronbach's alpha was 0.93.

Analysis of Phenotypic Data

Data were analyzed using IBM SPSS Statistics, version 29.0, and Mplus, version 6.11. Descriptive statistics and frequency distributions were generated for

sample characteristics and AFI scores. As previously described (Merriman et al., 2014), growth mixture modeling with robust maximum likelihood estimation was used to identify three latent classes of patients with distinct attentional function profiles. The current study used an extreme phenotype approach to compare the high versus low–moderate classes. This approach assumes that individuals whose phenotypes are the most different from one another (e.g., low versus high levels of symptoms) should be grouped for study (Pérez-Gracia et al., 2010). Differences between the two classes in demographic and clinical characteristics were evaluated using parametric and nonparametric tests. A p value of less than 0.05 was considered statistically significant.

Analysis of Genomic Data

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

Single nucleotide polymorphism selection: A combination of tagging single nucleotide polymorphisms (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 155 SNPs among the 10 candidate genes passed all quality control filters and were included in the genetic association analyses. The SNPs among the 10 candidate genes were identified as follows:

- Voltage-gated potassium channel subfamily A member 1: one SNP
- Voltage-gated potassium channel subfamily D member 2: nine SNPs
- Voltage-gated potassium channel modifier subfamily S member 1: four SNPs
- Inwardly rectifying potassium channel subfamily J member 3 (*KCNJ3*): 28 SNPs
- Inwardly rectifying potassium channel subfamily J member 5 (*KCNJ5*): eight SNPs
- Inwardly rectifying potassium channel subfamily J member 6 (*KCNJ6*): 58 SNPs
- Inwardly rectifying potassium channel subfamily J member 9: two SNPs
- Two-pore domain potassium channel subfamily K member 2 (*KCNK2*): 22 SNPs
- Two-pore domain potassium channel subfamily K member 3 (*KCNK3*): six SNPs
- Two-pore domain potassium channel subfamily K member 9 (*KCNK9*): 17 SNPs

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).

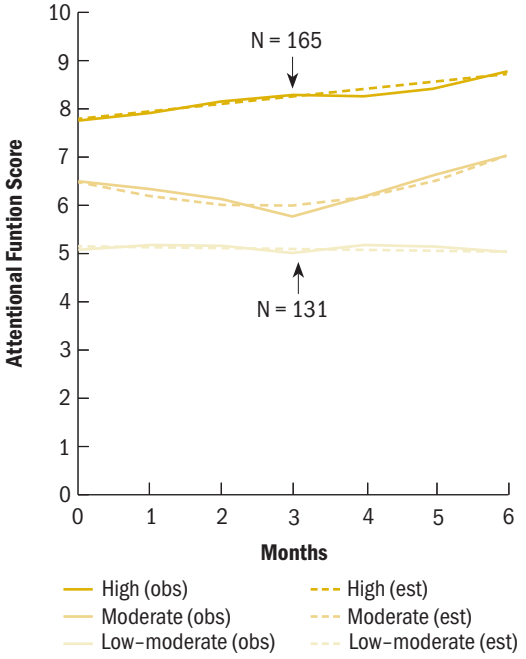
For association tests, the following three genetic models were assessed for each SNP: additive, dominant, and recessive using chi-square or Fisher's exact tests. For the significant SNPs, the genetic model that best fit the data, by maximizing the significance of the p value, was selected for the multivariate analysis. Logistic regression analyses, which controlled for significant covariates as well as genomic estimates of and self-reported race and ethnicity, were used to evaluate the association between SNPs and haplotypes that were significant in the bivariate analyses and membership in the low–moderate attentional function class. A backward stepwise regression 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 fit and unadjusted and covariate-adjusted odds ratios were estimated using Stata, version 15.

Results

Growth Mixture Modeling Analysis for Attentional Function

As previously described (Merriman et al., 2014), three classes with distinct attentional function profiles were identified in patients with breast cancer who were assessed prior to and for six months after surgery using growth mixture modeling. Patients in the high attentional function (high) class (N = 165, 42%) had an estimated AFI score of 7.78 at enrollment, which increased and remained high during the next six months. Patients in the moderate attentional function

FIGURE 1. Attentional Function Profiles for Patients in Each of the Latent Classes



est—estimated; obs—observed

Note. Arrows indicate the 2 latent classes used in the genomic analyses.

Note. Self-reported cancer-related cognitive impairment was assessed using the Attentional Function Index. Higher mean scores on a numeric rating scale ranging from 0 to 10 indicate greater capacity to direct attention.

(moderate) class (N = 101, 25%) had an estimated AFI score of 6.58 at enrollment, which decreased and then increased significantly but remained moderate during the next six months. Patients in the low–moderate attentional function (low–moderate) class (N = 131, 33%) had an estimated AFI score of 5.23 at enrollment, which did not change significantly during the next six months. In the current study, which used an extreme phenotype approach (Pérez-Gracia et al., 2010), differences between patients in the high (N = 165, 56%) and low–moderate (N = 131, 44%) classes were evaluated (see Figure 1).

Demographic and Clinical Characteristics

Compared to the high class, the low–moderate class was aged younger and had a lower annual income, a higher body mass index, a higher comorbidity burden, and a lower functional status. In addition, they were more likely to have received neoadjuvant therapy (see Table 1).

Candidate Gene Analysis

As shown in Supplemental Table 1 online, genotype frequencies were significantly different between the attentional function classes for 15 SNPs and 4 haplotypes (i.e., inwardly rectifying potassium channel subfamily J member 3 [*KCNJ3*]: 1 SNP, *KNCJ5*: 1 SNP, *KCNJ6*: 6 SNPs and 2 haplotypes, *KCNK2*: 4 SNPs and 1 haplotype, two-pore domain potassium channel subfamily K member 3 [*KCNK3*]: 1 SNP and 1 haplotype, and *KCNK9*: 2 SNPs).

Regression Analyses

To better estimate the magnitude (odds ratio) and precision (confidence interval) of genotype on attentional function class membership, multivariate logistic regression models were fit. In the final regression analyses of the phenotypic characteristics that were evaluated (i.e., age, annual income, body mass index, functional status, comorbidity burden, and receipt of neoadjuvant treatment), which included self-reported and genomic estimates of race and ethnicity, the only ones that were retained in the final model were age, comorbidity burden, and functional status. Six SNPs in four different genes remained significant in the logistic regressions (see Table 2).

For *KCNJ5* rs2846700, carrying one or two doses of the rare allele (AA versus AG + GG) was associated with a 57% decrease in the odds of belonging to the low–moderate class. For *KCNJ6* rs1399596, carrying two doses of the rare allele (TT + TC versus CC) was associated with a 77% decrease in the odds of belonging to the low–moderate class. For *KCNJ6* rs2835945, carrying two doses of the rare allele (GG + GA versus AA) was associated with a 2.53 fold increase in the odds of belonging to the low–moderate class (see Figure 2).

For *KCNK2* rs12757222, carrying one or two doses of the rare allele (AA versus AG + GG) was associated with a 62% decrease in the odds of belonging to the low–moderate class. For *KCNK2* rs12080135, carrying one or two doses of the rare allele (TT versus TG + GG) was associated with a 2.05 fold increase in the odds of belonging to the low–moderate class. For *KCNK9* rs3780051, carrying two doses of the rare allele (AA + AG versus GG) was associated with a 3.1 fold increase in the odds of belonging to the low–moderate class (see Figure 3).

Discussion

This study is the first to report on associations between self-reported CRCI and polymorphisms

TABLE 1. Differences in Demographic and Clinical Characteristics Between Patients in the High Versus Low–Moderate Attentional Function Classes Prior to Surgery

	High (N = 165)		Low–Moderate (N = 131)		
Demographic Characteristics	**$\bar{X}$**	**SD**	**$\bar{X}$**	**SD**	**Statistics**
Age (years)	56.7	11.2	52.6	12.6	t = 3.01, p = 0.003
Education (years)	15.8	2.7	15.6	2.4	t = 0.68, p = 0.498
Demographic Characteristics	**n**	**%**	**n**	**%**	**Statistics**
Race and ethnicity					χ^2 = 6.46, p = 0.091
Asian and Pacific Islander	17	10	19	15	
Black	15	9	18	14	
Hispanic, mixed, or another race	18	11	22	17	
White	113	69	72	55	
Living, marital, and employment status[a]					
Live alone	39	24	36	28	FE, p = 0.502
Married or partnered	69	42	60	46	FE, p = 0.554
Currently employed	84	52	53	41	FE, p = 0.077
Annual household income ($)					U, p = 0.002
Less than 30,000	19	14	36	34	
30,000–99,999	61	46	40	38	
100,000 or more	53	40	30	28	
Exercise status[a]					
Exercises regularly	118	72	82	64	FE, p = 0.166
Clinical Characteristics	**$\bar{X}$**	**SD**	**$\bar{X}$**	**SD**	**Statistics**
Body mass index (kg/m^2)	25.9	5.7	27.4	6.3	t = –2.26, p = 0.024
Karnofsky Performance Status Scale score	95.7	8.6	88.8	12.8	t = 5.25, p < 0.001
Self-Administered Comorbidity Questionnaire score	3.8	2.5	5.1	3.2	t = –3.83, p < 0.001
Clinical Characteristics	**n**	**%**	**n**	**%**	**Statistics**
Menopausal status[a]					
Postmenopausal	106	65	78	61	FE, p = 0.462
Stage of disease					U, p = 0.052
0	33	20	22	17	
I	67	41	42	32	
II	54	33	52	40	
III–IV	11	7	15	12	
Treatment-related characteristics[a]					
Received neoadjuvant therapy	27	16	35	27	FE, p = 0.032
Received HRT prior to surgery	22	13	21	16	FE, p = 0.511

[a]The n values per characteristic do not add up to the total N because only patients who answered "yes" are included.
FE—Fisher's exact test; HRT—hormone replacement therapy; U—Mann–Whitney U test
Note. Scores on the Karnofsky Performance Status Scale range from 30 ("I feel severely disabled and need to be hospitalized") to 100 ("I feel normal; I have no complaints or symptoms"). Scores on the Self-Administered Comorbidity Questionnaire range from 0 to 39, with higher scores indicating a greater comorbidity burden.
Note. Because of rounding, percentages may not total 100.

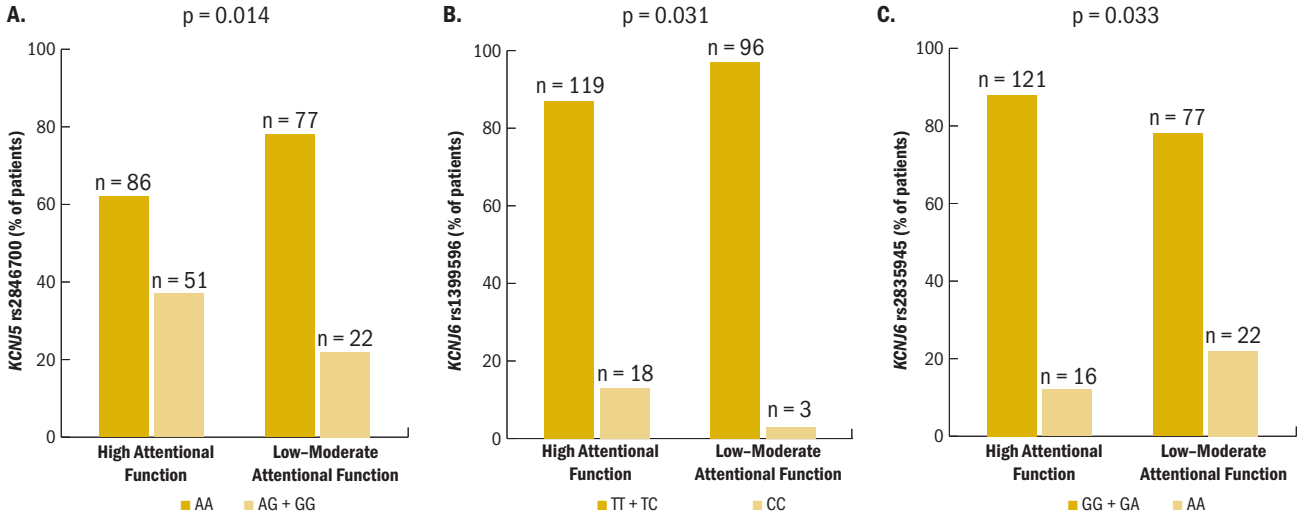
for potassium channel genes in patients with breast cancer who were assessed prior to and for six months after surgery. The latent classes were named based on the instrument's name (i.e., AFI), with its emphasis

TABLE 2. Multiple Logistic Regression Analyses for Single Nucleotide Polymorphisms in Potassium Channel Genes and Low–Moderate Attentional Function Class Membership

Predictor	Adj OR	SE	95% CI	Z	p
Inwardly rectifying potassium channels					
KCNJ5 rs2846700	0.43	0.15	[0.222, 0.847]	–2.45	0.014
Age	0.96	0.01	[0.937, 0.99]	–2.65	0.008
KPS score	0.96	0.02	[0.934, 0.993]	–2.38	0.017
SCQ score	1.17	0.07	[1.035, 1.323]	2.51	0.012
Overall model fit: $\chi^2 = 40.77$, $p < 0.001$, and pseudo $R^2 = 0.131$					
KCNJ6 rs1399596	0.23	0.16	[0.06, 0.91]	–2.1	0.036
KCNJ6 rs2835945	2.53	1.06	[1.116, 5.748]	2.22	0.026
Age	0.97	0.01	[0.941, 0.994]	–2.37	0.018
KPS score	0.96	0.02	[0.931, 0.991]	–2.51	0.012
SCQ score	1.17	0.07	[1.034, 1.324]	2.49	0.013
Overall model fit: $\chi^2 = 45.34$, $p < 0.001$, and pseudo $R^2 = 0.145$					
2-pore domain potassium channels					
KCNK2 rs12757222	0.38	0.13	[0.191, 0.736]	–2.85	0.004
KCNK2 rs12080135	2.05	0.67	[1.084, 3.872]	2.21	0.027
Age	0.96	0.01	[0.935, 0.99]	–2.64	0.008
KPS score	0.96	0.02	[0.935, 0.996]	–2.24	0.025
SCQ score	1.21	0.08	[1.069, 1.374]	3	0.003
Overall model fit: $\chi^2 = 51.21$, $p < 0.001$, and pseudo $R^2 = 0.164$					
KCNK9 rs3780051	3.1	1.09	[1.554, 6.186]	3.21	0.001
Age	0.97	0.01	[0.94, 0.993]	–2.43	0.015
KPS score	0.96	0.02	[0.934, 0.993]	–2.39	0.017
SCQ score	1.21	0.08	[1.071, 1.372]	3.05	0.002
Overall model fit: $\chi^2 = 45.19$, $p < 0.001$, and pseudo $R^2 = 0.145$					

adj—adjusted; CI—confidence interval; *KCNJ5*—inwardly rectifying potassium channel subfamily J member 5; *KCNJ6*—inwardly rectifying potassium channel subfamily J member 6; *KCNK9*—2-pore domain potassium channel subfamily K member 9; *KCNK2*—2-pore domain potassium channel subfamily K member 2; KPS—Karnofsky Performance Status Scale; OR—odds ratio; SCQ—Self-Administered Comorbidity Questionnaire; SE—standard error
Note. This table depicts the multiple logistic regression analyses of candidate gene associations with low–moderate attentional function class membership. For each model, the first 3 principal components identified from the analysis of ancestry informative markers, as well as self-reported race and ethnicity, were retained in all models to adjust for potential confounding because of race or ethnicity (data not shown). For the regression analyses, predictors evaluated in each model included genotype (*KCNJ5* rs2846700: AA versus AG + GG; *KCNJ6* rs1399596: TT + TC versus CC; *KCNJ6* rs2835945: GG + GA versus AA; *KCNK2* rs12757222: AA versus AG + GG; *KCNK2* rs12080135: TT versus TG + GG; *KCNK9* rs3780051: AA + AG versus GG) and age, KPS score, and SCQ score.

FIGURE 2. Differences in Genotype Distributions for the Inwardly Rectifying Potassium Channel Genes



KCNJ5—inwardly rectifying potassium channel subfamily J member 5; *KCNJ6*—inwardly rectifying potassium channel subfamily J member 6
Note. Figure A depicts differences between the latent classes in the percentages of patients who were homozygous for the common allele (AA) or heterozygous or homozygous for the rare allele (AG + GG) for rs2846700 in *KCNJ5*. Figure B depicts differences between the latent classes in the percentages of patients who were homozygous or heterozygous for the common allele (TT + TC) or homozygous for the rare allele (CC) for rs1399596 in *KCNJ6*. Figure C depicts differences between the latent classes in the percentages of patients who were homozygous or heterozygous for the common allele (GG + GA) or homozygous for the rare allele (AA) for rs2835945 in *KCNJ6*.

on attention. However, in addition to attention, the AFI assesses perceived effectiveness in performing daily activities that are supported by working memory and executive functions (e.g., setting goals, planning, carrying out tasks) (Cimprich et al., 2011). Therefore, it is a valid and reliable measure of self-reported CRCI.

In the final logistic regression model, risk factors associated with membership in the low–moderate class included younger age, a higher comorbidity burden, and a lower functional status. As noted in one systematic review (Kim et al., 2020), although the association between age and CRCI is among the most frequently evaluated characteristics, results are inconclusive. For example, in one study of cancer survivors (Schmidt et al., 2016), younger age was associated with the occurrence of self-reported CRCI in the bivariate analysis, but it did not remain significant in the multivariate analysis. The fact that a higher comorbidity burden and lower functional status remained significant in the multivariate model is not surprising given that CRCI is frequently associated with the presence of comorbid conditions (Zhou et al., 2024). In addition, the presence of multiple comorbid conditions is associated with worse functional status in patients with breast cancer (Chia et al., 2021).

Genomic Findings

Although specific functions vary by subtype, potassium channels regulate a number of biologic functions within the central nervous system, including the release of neurotransmitters, neuronal excitability, and plasticity (Djillani et al., 2019). Of the six significant SNPs identified in the current study, three were for inwardly rectifying potassium channel genes (i.e., *KCNJ5* rs2846700, *KCNJ6* rs1399596, and *KCNJ6* rs2835945), and three were for two-pore domain potassium channel genes (i.e., *KCNK2* rs12757222, *KCNK2* rs12080135, and *KCNK9* rs3780051). All of these SNPs are intron variants (Sherry et al., 2001). Although once believed to be noncoding and nonfunctional, evidence suggests that intron splicing is linked with the enhancement of transcription (Girardini et al., 2023). Of note, emerging evidence suggests that introns can regulate gene expression through intron-mediated enhancement of gene expression (Girardini et al., 2023).

Inwardly rectifying potassium channel genes: In terms of function, *KCNJ5* and *KCNJ6* are genes within the G-protein–gated inwardly rectifying potassium channel subfamily. G-protein–gated inwardly rectifying potassium channels regulate neuronal firing and excitability in the brain (Rifkin et al., 2017). Although

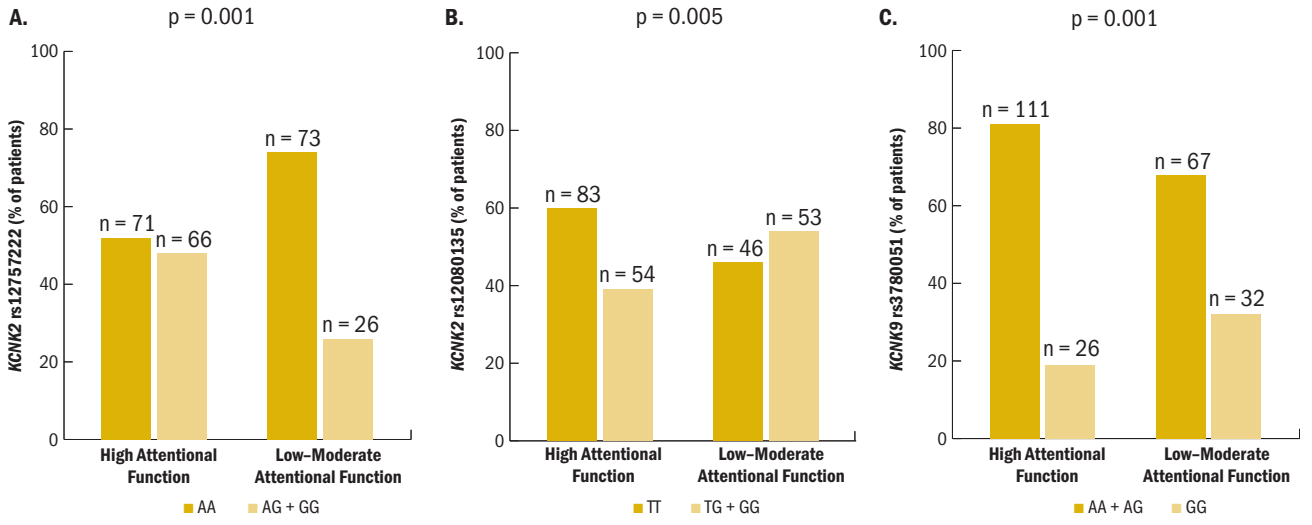
no human studies were identified that reported findings related to rs2846700 and CRCI, in a preclinical study (Wickman et al., 2000), *KCNJ5* knockout mice (i.e., mice lacking a functional *KCNJ5* gene) had worse performance on tests of spatial learning and memory compared to wild-type mice (i.e., mice with a functional *KCNJ5* gene).

An evaluation of expression quantitative trait loci for rs2846700 found associations with the pancreas (Lonsdale et al., 2013). Given that expression quantitative trait loci are a region of the chromosome where genetic variations are associated with the expression levels of nearby or distant genes (Zhang & Zhao, 2023), additional research is needed to understand this association. However, it is notable that in one study (Jongsma et al., 2011), decrements in cognitive function were worse in patients with chronic pancreatitis compared to healthy controls.

No studies were identified that reported findings for rs1399596 and rs2835945 and CRCI. However, in a preclinical model of Down syndrome (Kleschevnikov, 2022), triplication of the *KCNJ6* gene resulted in the development of abnormal neural circuits that caused cognitive impairment. In a case report of a patient with Keppen-Lubinsky syndrome (van Midden et al., 2023), variations in the *KCNJ6* gene were associated with a novel phenotype that included a mild intellectual disability. In terms of expression, the *KCNJ6* gene regulates the excitability of dopaminergic neurons and is expressed in brain regions associated with attention deficit hyperactivity disorder (Ziegler et al., 2020).

Two-pore domain potassium channel genes: Two-pore domain potassium channels are found throughout the central nervous system (e.g., neurons, brain endothelial cells) (Bittner et al., 2014). Although no studies were identified that reported findings for rs12757222 or rs12080135 and CRCI, the *KCNK2* gene encodes the potassium channel subfamily K member 2 (TREK-1). As noted in one review (Djillani et al., 2019), TREK-1 is expressed in the brain and has roles in a variety of clinical conditions (e.g., depression, ischemia, pain). In a mouse model of Alzheimer disease (Li et al., 2022), activation of TREK-1 channels with linolenic-α acid improved learning and memory deficits. In another preclinical study (Wang et al., 2020), knockout of TREK-1 expression in mice impaired the cellular structure and function of hippocampal pyramidal neurons. The authors concluded that cognitive impairment in conditions associated with aberrant expression of TREK-1 could be attributed to decrements in this potassium channel's ability to regulate

FIGURE 3. Differences in Genotype Distribution for the 2-Pore Domain Potassium Channel Genes



KCNK9—inwardly rectifying potassium channel subfamily J member 9; *KCNK2*—2-pore domain potassium channel subfamily K member 2
Note. Figure A depicts differences between the latent classes in the percentages of patients who were homozygous for the common allele (AA) or heterozygous or homozygous for the rare allele (AG + GG) for rs12757222 in *KCNK2*. Figure B depicts differences between the latent classes in the percentages of patients who were homozygous for the common allele (TT) or heterozygous or homozygous for the rare allele (TG + GG) for rs12080135 in *KCNK2*. Figure C depicts differences between the latent classes in the percentages of patients who were homozygous or heterozygous for the common allele (AA + AG) or homozygous for the rare allele (GG) for rs3780051 in *KCNK9*.

neuronal morphology, excitability, synaptic transmission, and plasticity (Wang et al., 2020).

Although no studies were identified that reported findings for rs3780051 and CRCI, a variant of the *KCNK9* gene is associated with Birk-Barel syndrome (Zadeh & Graham, 2017), a condition that includes delayed intellectual development. The *KCNK9* gene encodes a two-pore domain, acid-sensitive potassium channel (TASK3). As noted in one review (Bittner et al., 2010), TASK3 is critical for T-cell activation and subsequent inflammatory processes.

Limitations

Because this study is the first to evaluate for associations between self-reported CRCI and potassium channel genes in patients with breast cancer, the findings warrant confirmation in larger samples, as well as in men with prostate and testicular cancers, and in samples of patients with heterogeneous types of cancer. In addition, because CRCI was assessed using a self-report measure, future studies need to evaluate for associations between objective measures and potassium gene polymorphisms. Because a custom array was used in the parent study that evaluated other symptoms (e.g., pain), only a limited number of candidate genes were evaluated. Finally, given that no studies were identified that reported associations between CRCI and each of the significant SNPs in the current study, additional research is warranted on the role of various types of potassium channels in CRCI.

Implications for Nursing and Research

Although the findings from this research do not have immediate implications for clinical practice, they provide a foundation for ongoing research. First, the significant SNPs identified in this study were for either inwardly rectifying or two-pore domain potassium channel genes. Given the complex biologic roles of the various potassium channel genes, evaluation of other types of potassium channels, as well as other types of molecular analyses (e.g., gene expression, methylation), are warranted. Future studies should evaluate other genes that may affect cognitive function in patients with cancer (e.g., calcium channel genes [Baracaldo-Santamaría et al., 2023; Dhureja et al., 2023], sodium channel genes [Baumgartner et al., 2023; Noebels, 2019]). Genomic analyses that evaluate for associations with the subscales of the AFI (i.e., effective action, attentional lapses, and interpersonal effectiveness) may increase understanding of more specific CRCI phenotypes and/or mechanisms. Finally, future studies need to recruit a more diverse sample of patients, particularly in relation to various social determinants of health (e.g., neighborhood, insurance status, access to health care, occupation), which may affect cognitive function.

KNOWLEDGE TRANSLATION

- Self-reported changes in cognitive function are common in patients with breast cancer.
- Polymorphisms for potassium channel genes were associated with self-reported cognitive changes.
- Information about genomic markers that contribute to cancer-related cognitive impairment can support the development of prevention and mitigation strategies.

Conclusion

Because ion channels represent 19% of human genome–derived proteins targeted by drugs (Santos et al., 2017), additional research on associations between CRCI and a variety of ion channels may lead to the development of new and individualized therapies to prevent or treat this symptom. This study provides novel information on associations between self-reported CRCI and potassium channel genes in patients with breast cancer who were assessed prior to and for six months after surgery. These findings can be used to guide future research on the mechanisms that underlie CRCI. Equally important, they may lead to the identification of patients at increased risk for CRCI and the development of novel interventions.

Kate R. Oppegaard, RN, PhD, OCN®, is a research fellow and **Marilyn J. Hammer, PhD, DC, RN, FAAN,** is the director of the Phyllis F. Cantor Center for Research in Nursing and Patient Care Services, both at the Dana-Farber Cancer Institute in Boston, MA; **Yvette P. Conley, PhD, FAAN,** is a professor and **Carolyn S. Harris, PhD, RN, BMTCN®, OCN®,** is a postdoctoral student, both in the School of Nursing at the University of Pittsburgh in Pennsylvania; **Bruce A. Cooper, PhD,** is a research data analyst III and senior statistician, and **Steven M. Paul, PhD,** is a research data analyst III, both in the Department of Physiological Nursing in the School of Nursing at the University of California, San Francisco; **Joosun Shin, PhD, RN, OCN®,** is a research fellow at the Dana-Farber Cancer Institute; and **Lisa Morse, MS, RN, CNS** is a postdoctoral student in the School of Nursing, **Gary M. Abrams, MD,** is a professor in the School of Medicine, **Jon D. Levine, PhD, MD,** is a professor in the Department of Oral and Maxillofacial Surgery in the School of Dentistry, and **Christine Miaskowski, PhD, RN,** is a professor in the Department of Physiological Nursing in the School of Nursing,

all at the University of California, San Francisco. Miaskowski can be reached at chris.miaskowski@ucsf.edu, with copy to ONFEditor@ons.org. (Submitted December 2023. Accepted February 14, 2024.)

This research was funded, in part, by grants from the National Cancer Institute (CA107091, CA118657). Oppegaard received postdoctoral fellowship support from the National Cancer Institute (CA156734). Harris received postdoctoral fellowship support from the National Institute of Nursing Research (NR009759). Shin received research funding from the Mittelman Family Fund Fellowship for Integrative Therapy. Hammer received research funding from GSK through Pack Health.

Oppegaard and Miaskowski contributed to the conceptualization and design. Abrams and Miaskowski completed the data collection. Cooper, Paul, and Miaskowski provided statistical support. Oppegaard, Conley, Harris, Cooper, Levine, and Miaskowski provided the analysis. Oppegaard, Hammer, Conley, Harris, Shin, Morse, Abrams, Levine, and Miaskowski contributed to the manuscript preparation.

REFERENCES

Alam, K.A., Svalastoga, P., Martinez, A., Glennon, J.C., & Haavik, J. (2023). Potassium channels in behavioral brain disorders. Molecular mechanisms and therapeutic potential: A narrative review. *Neuroscience and Biobehavioral Reviews, 152*, 105301. https://doi.org/10.1016/j.neubiorev.2023.105301

Arnsten, A.F.T., Ishizawa, Y., & Xie, Z. (2023). Scientific rationale for the use of α2A-adrenoceptor agonists in treating neuroinflammatory cognitive disorders. *Molecular Psychiatry, 28*(11), 4540–4552. https://doi.org/10.1038/s41380-023-02057-4

Bagnall-Moreau, C., Chaudhry, S., Salas-Ramirez, K., Ahles, T., & Hubbard, K. (2019). Chemotherapy-induced cognitive impairment is associated with increased inflammation and oxidative damage in the hippocampus. *Molecular Neurobiology, 56*(10), 7159–7172. https://doi.org/10.1007/s12035-019-1589-z

Baracaldo-Santamaría, D., Avendaño-Lopez, S.S., Ariza-Salamanca, D.F., Rodriguez-Giraldo, M., Calderon-Ospina, C.A., González-Reyes, R.E., & Nava-Mesa, M.O. (2023). Role of calcium modulation in the pathophysiology and treatment of Alzheimer's disease. *International Journal of Molecular Sciences, 24*(10), 9067. https://doi.org/10.3390/ijms24109067

Baumgartner, T.J., Haghighijoo, Z., Goode, N.A., Dvorak, N.M., Arman, P., & Laezza, F. (2023). Voltage-gated Na^+ channels in Alzheimer's disease: Physiological roles and therapeutic potential. *Life, 13*(8), 1655. https://doi.org/10.3390/life13081655

Bittner, S., Budde, T., Wiendl, H., & Meuth, S.G. (2010). From the background to the spotlight: TASK channels in pathological conditions. *Brain Pathology, 20*(6), 999–1009. https://doi.org/10.1111/j.1750-3639.2010.00407.x

Bittner, S., Ruck, T., Fernández-Orth, J., & Meuth, S.G. (2014). TREK-king the blood–brain–barrier. *Journal of Neuroimmune Pharmacology, 9*(3), 293–301. https://doi.org/10.1007/s11481-014-9530-8

Chia, Z., Parks, R.M., & Cheung, K.-L. (2021). Does breast cancer surgery impact functional status and independence in older patients? A narrative review. *Oncology and Therapy, 9*(2), 373–383. https://doi.org/10.1007/s40487-021-00170-4

Cimprich, B., Visovatti, M., & Ronis, D.L. (2011). The Attentional Function Index—A self-report cognitive measure. *Psycho-Oncology, 20*(2), 194–202. https://doi.org/10.1002/pon.1729

Dhureja, M., Arthur, R., Soni, D., Upadhayay, S., Temgire, P., & Kumar, P. (2023). Calcium channelopathies in neurodegenerative disorder: An untold story of RyR and SERCA. *Expert Opinion on Therapeutic Targets, 27*(11), 1159–1172. https://doi.org/10.1080/14728222.2023.2277863

Di, A., Xiong, S., Ye, Z., Malireddi, R.K.S., Kometani, S., Zhong, M., . . . Malik, A.B. (2018). The TWIK2 potassium efflux channel in macrophages mediates NLRP3 inflammasome-induced inflammation. *Immunity, 49*(1), 56–65.e4. https://doi.org/10.1016/j.immuni.2018.04.032

Djillani, A., Mazella, J., Heurteaux, C., & Borsotto, M. (2019). Role of TREK-1 in health and disease, Focus on the central nervous system. *Frontiers in Pharmacology, 10*, 379. https://doi.org/10.3389/fphar.2019.00379

Gabriel, S.B., Schaffner, S.F., Nguyen, H., Moore, J.M., Roy, J., Blumenstiel, B., . . . Altshuler, D. (2002). The structure of haplotype blocks in the human genome. *Science, 296*(5576), 2225–2229. https://doi.org/10.1126/science.1069424

Girardini, K.N., Olthof, A.M., & Kanadia, R.N. (2023). Introns: The "dark matter" of the eukaryotic genome. *Frontiers in Genetics, 14*, 1150212. https://doi.org/10.3389/fgene.2023.1150212

Halder, I., Shriver, M., Thomas, M., Fernandez, J.R., & Frudakis, T. (2008). A panel of ancestry informative markers for estimating individual biogeographical ancestry and admixture from four continents: Utility and applications. *Human Mutation, 29*(5), 648–658. https://doi.org/10.1002/humu.20695

Han, T.J., Felger, J.C., Lee, A., Mister, D., Miller, A.H., & Torres, M.A. (2016). Association of childhood trauma with fatigue, depression, stress, and inflammation in breast cancer patients undergoing radiotherapy. *Psycho-Oncology, 25*(2), 187–193. https://doi.org/10.1002/pon.3831

Humphries, E.S.A., & Dart, C. (2015). Neuronal and cardiovascular potassium channels as therapeutic drug targets: Promise and pitfalls. *Journal of Biomolecular Screening, 20*(9), 1055–1073. https://doi.org/10.1177/1087057115601677

Jongsma, M.L.A., Postma, S.A.E., Souren, P., Arns, M., Gordon, E., Vissers, K., . . . van Goor, H. (2011). Neurodegenerative properties of chronic pain: Cognitive decline in patients with chronic pancreatitis. *PLOS ONE, 6*(8), e23363. https://doi.org/10.1371/journal.pone.0023363

Karnofsky, D. (1977). *Performance scale*. Plenum Press.

Kim, H.-J., Jung, S.-O., Kim, H., & Abraham, I. (2020). Systematic

review of longitudinal studies on chemotherapy-associated subjective cognitive impairment in cancer patients. *Psycho-Oncology, 29*(4), 617–631. https://doi.org/10.1002/pon.5339

Kleschevnikov, A.M. (2022). Enhanced GIRK2 channel signaling in Down syndrome: A feasible role in the development of abnormal nascent neural circuits. *Frontiers in Genetics, 13*, 1006068. https://doi.org/10.3389/fgene.2022.1006068

Li, F., Zhou, S.-N., Zeng, X., Li, Z., Yang, R., Wang, X.-X., . . . Lu, L. (2022). Activation of the TREK-1 potassium channel improved cognitive deficits in a mouse model of Alzheimer's disease by modulating glutamate metabolism. *Molecular Neurobiology, 59*(8), 5193–5206. https://doi.org/10.1007/s12035-022-02776-9

Lonsdale, J. Thomas, J., Salvatore, M., Phillips, R., Lo, E., Shad, S., . . . Moore, H.F. (2013). The genotype-tissue expression (GTEx) project. *Nature Genetics, 45*(6), 580–585. https://doi.org/10.1038/ng.2653

Mayo, S.J., Lustberg, M., Dhillon, H.M., Nakamura, Z.M., Allen, D.H., Von Ah, D., . . . Peters, K.B. (2021). Cancer-related cognitive impairment in patients with non-central nervous system malignancies: An overview for oncology providers from the MASCC neurological complications study group. *Supportive Care in Cancer, 29*(6), 2821–2840. https://doi.org/10.1007/s00520-020-05860-9

Medzhitov, R. (2008). Origin and physiological roles of inflammation. *Nature, 454*(7203), 428–435. https://doi.org/10.1038/nature07201

Merriman, J.D., Aouizerat, B.E., Cataldo, J.K., Dunn, L., Cooper, B.A., West, C., . . . Miaskowski, C. (2014). Association between an interleukin 1 receptor, type I promoter polymorphism and self-reported attentional function in women with breast cancer. *Cytokine, 65*(2), 192–201. https://doi.org/10.1016/j.cyto.2013.11.003

Noebels, J.L. (2019). Predicting the impact of sodium channel mutations in human brain disease. *Epilepsia, 60*(Suppl. 3), S8–S16. https://doi.org/10.1111/epi.14724

Onzi, G.R., D'Agustini, N., Garcia, S.C., Guterres, S.S., Pohlmann, P.R., Rosa, D.D., & Pohlmann, A.R. (2022). Chemobrain in breast cancer: Mechanisms, clinical manifestations, and potential interventions. *Drug Safety, 45*(6), 601–621. https://doi.org/10.1007/s40264-022-01182-3

Oppegaard, K.R., Armstrong, T.S., Anguera, J.A., Kober, K.M., Kelly, D.L., Laister, R.C., . . . Mayo, S.J. (2022). Blood-based biomarkers of cancer-related cognitive impairment in non-central nervous system cancer: A scoping review. *Critical Reviews in Oncology/Hematology, 180*, 103822. https://doi.org/10.1016/j.critrevonc.2022.103822

Pérez-Gracia, J.L., Gúrpide, A., Ruiz-Ilundain, M.G., Alfaro Alegría, C., Colomer, R., García-Foncillas, J., & Melero Bermejo, I. (2010). Selection of extreme phenotypes: The role of clinical observation in translational research. *Clinical and Translational Oncology, 12*(3), 174–180. https://doi.org/10.1007/s12094-010-0487-7

Rifkin, R.A., Moss, S.J., & Slesinger, P.A. (2017). G protein–gated potassium channels: A link to drug addiction. *Trends in Pharmacological Sciences, 38*(4), 378–392. https://doi.org/10.1016/j.tips.2017.01.007

Sangha, O., Stucki, G., Liang, M.H., Fossel, A.H., & Katz, J.N. (2003). The Self-Administered Comorbidity Questionnaire: A new method to assess comorbidity for clinical and health services research. *Arthritis and Rheumatism, 49*(2), 156–163. https://doi.org/10.1002/art.10993

Santos, R., Ursu, O., Gaulton, A., Bento, A.P., Donadi, R.S., Bologa, C.G., . . . Overington, J.P. (2017). A comprehensive map of molecular drug targets. *Nature Reviews. Drug Discovery, 16*(1), 19–34. https://doi.org/10.1038/nrd.2016.230

Schmidt, J.E., Beckjord, E., Bovbjerg, D.H., Low, C.A., Posluszny, D.M., Lowery, A.E., . . . Rechis, R. (2016). Prevalence of perceived cognitive dysfunction in survivors of a wide range of cancers: Results from the 2010 LIVESTRONG survey. *Journal of Cancer Survivorship, 10*(2), 302–311. https://doi.org/10.1007/s11764-015-0476-5

Sherry, S.T., Ward, M.H., Kholodov, M., Baker, J., Phan, L., Smigielski, E.M., & Sirotkin, K. (2001). dbSNP: The NCBI database of genetic variation. *Nucleic Acids Research, 29*(1), 308–311. https://doi.org/10.1093/nar/29.1.308

Singh, N., Baby, D., Rajguru, J.P., Patil, P.B., Thakkannavar, S.S., & Pujari, V.B. (2019). Inflammation and cancer. *Annals of African Medicine, 18*(3), 121–126. https://doi.org/10.4103/aam.aam_56_18

Stephens, M., Smith, N.J., & Donnelly, P. (2001). A new statistical method for haplotype reconstruction from population data. *American Journal of Human Genetics, 68*(4), 978–989. https://doi.org/10.1086/319501

van Midden, V.M., Kinsley, L., Fraint, A., Krainc, D., & Mencacci, N.E. (2023). Expanding the spectrum of *KCNJ6*-related disorders: Milder phenotype with pathological startle responses. *Clinical Genetics, 103*(1), 103–108. https://doi.org/10.1111/cge.14226

Wang, W., Kiyoshi, C.M., Du, Y., Taylor, A.T., Sheehan, E.R., Wu, X., & Zhou, M. (2020). TREK-1 null impairs neuronal excitability, synaptic plasticity, and cognitive function. *Molecular Neurobiology, 57*(3), 1332–1346. https://doi.org/10.1007/s12035-019-01828-x

Weiss, S.J., Franck, L.S., Leutwyler, H., Dawson-Rose, C.S., Wallhagen, M.I., Staveski, S.L., . . . Miaskowski, C.A. (2023). Theory of symptom management. In M.J. Smith, P.R. Liehr, & R.D. Carpenter (Eds.), *Middle range theory for nursing* (5th ed., pp. 125–141). Springer.

Wickman, K., Karschin, C., Karschin, A., Picciotto, M.R., & Clapham, D.E. (2000). Brain localization and behavioral impact of the G-protein-gated K+ channel subunit GIRK4. *Journal of Neuroscience, 20*(15), 5608–5615. https://doi.org/10.1523/jneurosci.20-15-05608.2000

Zadeh, N., & Graham, J.M., Jr. (2017). *KCNK9* imprinting syndrome. In M.P. Adam, J. Feldman, G.M. Mirzaa, R.A. Pagon,

S.E. Wallace, L.J.H. Bean, . . . A. Amemiya (Eds.), *GeneReviews®*. https://www.ncbi.nlm.nih.gov/books/NBK425128

Zhang, J., & Zhao, H. (2023). eQTL studies: From bulk tissues to single cells. *Journal of Genetics and Genomics, 50*(12), 925–933. https://doi.org/10.1016/j.jgg.2023.05.003

Zhou, X., Zhang, X., Zhong, T., Zhou, M., Gao, L., & Chen, L. (2024). Prevalence and associated factors of chemotherapy-related cognitive impairment in older breast cancer survivors. *Journal of Advanced Nursing, 80*(2), 484–499. https://doi.org/10.1111/jan.15842

Ziegler, G.C., Röser, C., Renner, T., Hahn, T., Ehlis, A.-C., Weber, H., . . . Lesch, K.-P. (2020). *KCNJ6* variants modulate reward-related brain processes and impact executive functions in attention-deficit/hyperactivity disorder. *American Journal of Medical Genetics Part B Neuropsychiatric Genetics, 183*(5), 247–257. https://doi.org/10.1002/ajmg.b.32734

SUPPLEMENTAL TABLE 1. Summary of SNPs Analyzed for Potassium Channel Genes Between the High and Low–Moderate Attentional Function Classes

Gene	SNP	Position	Chr	MAF	Alleles	χ^2	p	Model
Voltage-gated potassium channels								
KCNA1	rs4766311	48926991	1	0.466	C > T	0.32	0.852	A
KCND2	rs17376373	119787721	7	0.197	T > G	2.502	0.286	A
KCND2	rs702414	119924204	7	0.249	G > C	2.819	0.244	A
KCND2	rs802340	119975021	7	0.293	G > T	4.681	0.096	A
KCND2	rs12706292	120012310	7	0.346	A > G	3.371	0.185	A
KCND2	rs4730967	120060462	7	0.32	T > C	2.941	0.23	A
KCND2	rs1072198	120114585	7	0.304	A > G	1.92	0.383	A
KCND2	rs11489533	120117902	7	0.268	A > G	3.337	0.189	A
KCND2	rs4727914	120122574	7	0.343	A > G	3.794	0.15	A
KCND2	rs12673992	120160059	7	0.319	A > G	3.12	0.21	A
KCND2	HapA1					3.096	0.213	
KCND2	HapA3					3.794	0.15	
KCNS1	rs4499491	43154833	20	0.432	C > A	3.693	0.158	A
KCNS1	rs6124684	43154907	20	0.223	C > T	0.217	0.897	A
KCNS1	rs734784	43157041	20	0.447	A > G	1.048	0.592	A
KCNS1	rs6073643	43161484	20	0.274	T > C	2.962	0.227	A
KCNS1	HapA1					3.693	0.158	
KCNS1	HapA2					0.312	0.856	
KCNS1	HapA3					0.217	0.897	
KCNS1	HapB1					1.048	0.592	
KCNS1	HapB2					4.643	0.098	
KCNS1	HapB3					2.962	0.227	
Inwardly rectifying potassium channels								
KCNJ3	rs6435329	155265893	2	0.445	G > T	5.12	0.077	A
KCNJ3	rs3111020	155275635	2	0.45	T > C	0.155	0.925	A
KCNJ3	rs11895478	155279369	2	0.246	C > T	0.707	0.702	A
KCNJ3	rs3106653	155283806	2	0.262	A > C	2.266	0.322	A
KCNJ3	rs3111003	155300413	2	0.465	C > T	0.681	0.712	A
KCNJ3	rs3111006	155302345	2	0.375	C > T	1.092	0.579	A
KCNJ3	rs12471193	155304383	2	0.343	A > G	2.444	0.295	A

Continued on the next page

SUPPLEMENTAL TABLE 1. Summary of SNPs Analyzed for Potassium Channel Genes Between the High and Low–Moderate Attentional Function Classes *(Continued)*

Gene	SNP	Position	Chr	MAF	Alleles	χ^2	p	Model
Inwardly rectifying potassium channels *(continued)*								
KCNJ3	rs6711727	155304684	2	0.485	G > A	1.196	0.55	A
KCNJ3	rs2652443	155313983	2	0.395	G > A	1.253	0.534	A
KCNJ3	rs7574878	155315394	2	0.429	T > G	0.331	0.848	A
KCNJ3	rs2121085	155315711	2	0.447	A > G	1.032	0.597	A
KCNJ3	rs2121089	155317633	2	0.479	C > A	1.471	0.479	A
KCNJ3	rs2961959	155326068	2	0.432	C > G	1.129	0.569	A
KCNJ3	rs2591168	155326179	2	0.316	A > G	1.381	0.501	A
KCNJ3	rs2591172	155330423	2	0.333	T > G	0.213	0.899	A
KCNJ3	rs12995382	155340539	2	0.29	T > C	0.646	0.724	A
KCNJ3	rs13398937	155348593	2	0.362	C > G	3.035	0.219	A
KCNJ3	rs13390038	155351011	2	0.403	G > A	0.209	0.901	A
KCNJ3	rs12616121	155353928	2	0.469	A > G	0.555	0.758	A
KCNJ3	rs2591158	155355912	2	0.28	A > C	0.087	0.957	A
KCNJ3	rs2591157	155356612	2	0.33	A > G	3.379	0.185	A
KCNJ3	rs717175	155356841	2	0.332	C > T	FE	0.023	R
KCNJ3	rs1037091	155360603	2	0.375	G > A	1.518	0.468	A
KCNJ3	rs17641121	155373998	2	0.259	T > C	0.488	0.783	A
KCNJ3	rs2591173	155395322	2	0.477	C > A	0.017	0.992	A
KCNJ3	rs2971902	155400624	2	0.22	G > T	0.158	0.924	A
KCNJ3	rs2937600	155411014	2	0.299	A > G	1.249	0.536	A
KCNJ3	rs4467223	155414657	2	0.479	T > A	0.984	0.611	A
KCNJ3	HapA1					2.717	0.257	
KCNJ3	HapA2					0.707	0.702	
KCNJ3	HapA3					0.155	0.925	
KCNJ3	HapB1					0.661	0.718	
KCNJ3	HapB4					1.819	0.403	
KCNJ3	HapC3					1.653	0.438	
KCNJ3	HapC5					2.905	0.234	
KCNJ3	HapD1					1.953	0.377	
KCNJ3	HapD4					0.855	0.652	

Continued on the next page

SUPPLEMENTAL TABLE 1. Summary of SNPs Analyzed for Potassium Channel Genes Between the High and Low–Moderate Attentional Function Classes *(Continued)*

Gene	SNP	Position	Chr	MAF	Alleles	χ^2	p	Model
Inwardly rectifying potassium channels *(continued)*								
KCNJ3	HapE1					0.091	0.955	
KCNJ3	HapE2					2.503	0.286	
KCNJ3	HapE4					1.256	0.534	
KCNJ3	HapF1					2.417	0.299	
KCNJ3	HapF2					0.334	0.846	
KCNJ3	HapF4					0.074	0.964	
KCNJ3	HapG1					2.405	0.3	
KCNJ3	HapG3					0.195	0.907	
KCNJ3	HapG4					0.002	0.999	
KCNJ5	rs7941582	128266885	11	0.408	A > G	1.164	0.559	A
KCNJ5	rs2846700	128274148	11	0.172	A > G	FE	0.015	D
KCNJ5	rs4937384	128285012	11	0.223	T > C	1.912	0.385	A
KCNJ5	rs11221503	128277662	11	0.184	C > T	0.177	0.915	A
KCNJ5	rs2604212	128278165	11	0.459	C > G	1.160	0.56	A
KCNJ5	rs4937387	128278623	11	0.257	T > C	1.435	0.488	A
KCNJ5	rs11221510	128285907	11	0.241	A > T	1.734	0.42	A
KCNJ5	rs6590357	128286549	11	0.163	C > T	0.093	0.955	A
KCNJ5	HapA1					1.379	0.502	
KCNJ5	HapA2					0.18	0.914	
KCNJ5	HapA5					0.055	0.973	
KCNJ6	rs860795	37937160	21	0.208	G > C	0.936	0.626	A
KCNJ6	rs1709838	37941983	21	0.431	C > A	0.18	0.914	A
KCNJ6	rs10483038	37946641	21	0.279	T > C	0.313	0.855	A
KCNJ6	rs857967	37954006	21	0.197	T > A	2.271	0.321	A
KCNJ6	rs2835885	37961436	21	0.432	T > G	1.966	0.374	A
KCNJ6	rs858010	37987109	21	0.166	G > A	0.9	0.638	A
KCNJ6	rs1005546	37990742	21	0.45	C > T	0.519	0.771	A
KCNJ6	rs858003	37994854	21	0.197	C > T	2.422	0.298	A
KCNJ6	rs1709816	37999129	21	0.39	G > T	0.666	0.717	A
KCNJ6	rs13049947	38002710	21	0.403	C > T	0.692	0.707	A

Continued on the next page

SUPPLEMENTAL TABLE 1. Summary of SNPs Analyzed for Potassium Channel Genes Between the High and Low–Moderate Attentional Function Classes *(Continued)*

Gene	SNP	Position	Chr	MAF	Alleles	χ^2	p	Model
Inwardly rectifying potassium channels *(continued)*								
KCNJ6	rs2835914	38020720	21	0.347	G > C	3.726	0.155	A
KCNJ6	rs858035	38021061	21	0.344	T > C	0.751	0.687	A
KCNJ6	rs13048511	38037731	21	0.468	A > G	FE	0.013	D
KCNJ6	rs2835925	38041173	21	0.176	A > G	0.814	0.666	A
KCNJ6	rs857989	38042001	21	0.115	G > C	FE	0.033	D
KCNJ6	rs2835931	38043518	21	0.282	C > T	FE	0.025	D
KCNJ6	rs1399596	38045382	21	0.260	T > C	FE	0.009	R
KCNJ6	rs2835942	38052778	21	0.303	C > T	3.305	0.192	A
KCNJ6	rs2835945	38057170	21	0.398	G > A	FE	0.033	R
KCNJ6	rs1160350	38065897	21	0.494	G > C	2.539	0.281	A
KCNJ6	rs762145	38068188	21	0.366	C > T	FE	0.023	D
KCNJ6	rs2226356	38075902	21	0.427	C > T	3.252	0.197	A
KCNJ6	rs1787337	38077824	21	0.494	A > G	1.238	0.539	A
KCNJ6	rs2835961	38083028	21	0.482	G > A	1.276	0.528	A
KCNJ6	rs2835976	38103779	21	0.385	C > T	3.599	0.165	A
KCNJ6	rs2835977	38104067	21	0.224	G > A	0.6	0.741	A
KCNJ6	rs2211842	38105403	21	0.376	C > A	0.492	0.782	A
KCNJ6	rs2211843	38106055	21	0.234	G > T	0.977	0.614	A
KCNJ6	rs2211845	38106371	21	0.447	T > C	3.337	0.189	A
KCNJ6	rs2835982	38110247	21	0.368	C > A	2.385	0.303	A
KCNJ6	rs2835983	38110476	21	0.304	G > A	0.33	0.848	A
KCNJ6	rs2835984	38110657	21	0.497	A > T	0.948	0.622	A
KCNJ6	rs3787835	38111440	21	0.455	C > T	0.157	0.925	A
KCNJ6	rs6517435	38117092	21	0.422	G > A	0.499	0.779	A
KCNJ6	rs2154556	38120757	21	0.344	T > C	2.507	0.285	A
KCNJ6	rs4817896	38123831	21	0.248	C > T	0.553	0.758	A
KCNJ6	rs3787840	38124263	21	0.139	C > T	0.732	0.693	A
KCNJ6	rs991985	38128024	21	0.286	C > A	3.063	0.216	A
KCNJ6	rs2836007	38128761	21	0.194	C > T	3.2	0.202	A
KCNJ6	rs2836013	38132582	21	0.292	C > T	2.246	0.325	A

Continued on the next page

SUPPLEMENTAL TABLE 1. Summary of SNPs Analyzed for Potassium Channel Genes Between the High and Low–Moderate Attentional Function Classes *(Continued)*

Gene	SNP	Position	Chr	MAF	Alleles	χ^2	p	Model
Inwardly rectifying potassium channels *(continued)*								
KCNJ6	rs2836016	38134890	21	0.411	A > G	0.244	0.885	A
KCNJ6	rs2836019	38136864	21	0.327	C > T	3.809	0.149	A
KCNJ6	rs915800	38138203	21	0.455	C > T	0.311	0.856	A
KCNJ6	rs2226741	38146803	21	0.147	A > G	1.111	0.574	A
KCNJ6	rs7276928	38147607	21	0.288	G > A	3.787	0.151	A
KCNJ6	rs3827199	38149472	21	0.408	G > A	1.504	0.471	A
KCNJ6	rs4816585	38151120	21	0.495	G > A	0.501	0.778	A
KCNJ6	rs9305628	38166861	21	0.227	A > G	1.038	0.595	A
KCNJ6	rs9974219	38168568	21	0.277	A > T	1.154	0.561	A
KCNJ6	rs7277957	38168770	21	0.492	A > G	2.239	0.326	A
KCNJ6	rs1892682	38169935	21	0.265	G > A	0.501	0.778	A
KCNJ6	rs928765	38173472	21	0.292	C > T	0.157	0.925	A
KCNJ6	rs3787862	38174571	21	0.197	G > A	3.676	0.159	A
KCNJ6	rs10775660	38175388	21	0.415	C > T	0.034	0.983	A
KCNJ6	rs8129919	38176410	21	0.471	G > A	1.371	0.504	A
KCNJ6	rs2836039	38188930	21	0.195	G > A	NA	NA	NA
KCNJ6	rs2836048	38206168	21	0.321	G > A	1.956	0.376	A
KCNJ6	rs2836050	38206705	21	0.227	C > T	2.823	0.244	A
KCNJ6	rs3787870	38207323	21	0.463	A > G	0.052	0.974	A
KCNJ6	HapA1					0.405	0.817	
KCNJ6	HapA2					0.261	0.878	
KCNJ6	HapA3					0.984	0.611	
KCNJ6	HapB1					1.32	0.517	
KCNJ6	HapB2					2.271	0.321	
KCNJ6	HapB3					0.313	0.855	
KCNJ6	HapC1					0.519	0.771	
KCNJ6	HapC2					0.573	0.751	
KCNJ6	HapC3					0.9	0.638	
KCNJ6	HapD1					0.351	0.839	
KCNJ6	HapD4					0.213	0.899	

Continued on the next page

SUPPLEMENTAL TABLE 1. Summary of SNPs Analyzed for Potassium Channel Genes Between the High and Low–Moderate Attentional Function Classes *(Continued)*

Gene	SNP	Position	Chr	MAF	Alleles	χ^2	p	Model
Inwardly rectifying potassium channels *(continued)*								
KCNJ6	HapD6					2.178	0.337	
KCNJ6	HapE1					7.435	0.024	
KCNJ6	HapE2					4.971	0.083	
KCNJ6	HapE5					5.096	0.078	
KCNJ6	HapE7					0.788	0.674	
KCNJ6	HapF1					5.12	0.077	
KCNJ6	HapF2					6.888	0.032	
KCNJ6	HapF4					4.165	0.125	
KCNJ6	HapG1					1.628	0.443	
KCNJ6	HapG5					1.98	0.372	
KCNJ6	HapG6					0.163	0.922	
KCNJ6	HapH1					0.382	0.826	
KCNJ6	HapH3					2.036	0.361	
KCNJ6	HapH5					0.859	0.651	
KCNJ6	HapI1					2.821	0.244	
KCNJ6	HapI5					0.655	0.721	
KCNJ6	HapJ1					1.001	0.606	
KCNJ6	HapJ2					2.246	0.325	
KCNJ6	HapJ3					3.136	0.208	
KCNJ6	HapK1					0.311	0.856	
KCNJ6	HapK4					3.766	0.152	
KCNJ6	HapL1					1.247	0.536	
KCNJ6	HapL4					1.096	0.578	
KCNJ6	HapL5					1.038	0.595	
KCNJ6	HapM1					0.004	0.998	
KCNJ6	HapM4					3.003	0.223	
KCNJ6	HapM6					0.157	0.925	
KCNJ6	HapN2					3.13	0.209	
KCNJ6	HapN3					1.238	0.539	
KCNJ9	rs6677510	158318743	1	0.442	A > G	0.435	0.804	A

Continued on the next page

SUPPLEMENTAL TABLE 1. Summary of SNPs Analyzed for Potassium Channel Genes Between the High and Low–Moderate Attentional Function Classes *(Continued)*

Gene	SNP	Position	Chr	MAF	Alleles	χ^2	p	Model
Inwardly rectifying potassium channels *(continued)*								
KCNJ9	rs2753268	158324876	1	0.26	C > T	2.251	0.325	A
2-pore domain potassium channels								
KCNK2	rs2601640	213253979	1	0.492	A > G	2.213	0.331	A
KCNK2	rs12141327	213273537	1	0.335	G > A	1.83	0.401	A
KCNK2	rs1452619	213280153	1	0.12	A > G	0.76	0.684	A
KCNK2	rs10494991	213287222	1	0.331	T > C	1.603	0.449	A
KCNK2	rs1584759	213289445	1	0.453	A > C	1.196	0.55	A
KCNK2	rs12064317	213293664	1	0.136	G > T	0.115	0.944	A
KCNK2	rs6665177	213298091	1	0.155	G > A	0.471	0.79	A
KCNK2	rs12028008	213298169	1	0.497	A > G	0.981	0.612	A
KCNK2	rs12038094	213302819	1	0.291	C > T	0.075	0.963	A
KCNK2	rs17024179	213304166	1	0.163	T > C	0.625	0.732	A
KCNK2	rs7528988	213315040	1	0.259	C > T	2.618	0.27	A
KCNK2	rs2363561	213321930	1	0.395	C > T	3.849	0.146	A
KCNK2	rs12133857	213331109	1	0.128	G > T	FE	0.04	D
KCNK2	rs4411107	213355542	1	0.375	T > C	0.61	0.737	A
KCNK2	rs4303048	213385781	1	0.236	G > A	0.029	0.986	A
KCNK2	rs12757222	213391641	1	0.233	A > G	FE	< 0.001	D
KCNK2	rs1556905	213428215	1	0.411	C > A	0.851	0.653	A
KCNK2	rs10494994	213428830	1	0.207	G > A	1.044	0.593	A
KCNK2	rs12038695	213444580	1	0.494	A > C	FE	0.02	D
KCNK2	rs2027320	213446566	1	0.385	G > A	2.677	0.262	A
KCNK2	rs12143625	213458463	1	0.235	T > C	0.15	0.928	A
KCNK2	rs12080135	213463166	1	0.252	T > G	FE	0.035	D
KCNK2	HapA1					1.83	0.401	
KCNK2	HapA4					2.213	0.331	
KCNK2	HapB1					1.16	0.56	
KCNK2	HapB4					1.434	0.488	
KCNK2	HapC1					1.537	0.464	
KCNK2	HapC4					1.52	0.468	

Continued on the next page

SUPPLEMENTAL TABLE 1. Summary of SNPs Analyzed for Potassium Channel Genes Between the High and Low–Moderate Attentional Function Classes *(Continued)*

Gene	SNP	Position	Chr	MAF	Alleles	χ^2	p	Model
2-pore domain potassium channels *(continued)*								
KCNK2	HapC5					0.981	0.612	
KCNK2	HapD1					0.152	0.927	
KCNK2	HapD3					3.849	0.146	
KCNK2	HapE1					0.643	0.725	
KCNK2	HapE3					0.663	0.718	
KCNK2	HapE4					0.941	0.625	
KCNK2	HapF2					2.677	0.262	
KCNK2	HapF3					6.035	0.049	
KCNK3	rs1275982	26772593	2	0.497	C > T	0.149	0.928	A
KCNK3	rs1275977	26776359	2	0.414	A > G	1.238	0.538	A
KCNK3	rs11126666	26782315	2	0.33	G > A	3.603	0.165	A
KCNK3	rs1662987	26791686	2	0.243	A > G	2.592	0.274	A
KCNK3	rs1662988	26793738	2	0.29	C > T	0.097	0.953	A
KCNK3	rs7584568	26798797	2	0.471	G > A	6.801	0.033	A
KCNK3	HapA1					3.603	0.165	
KCNK3	HapA4					0.149	0.928	
KCNK3	HapB1					6.205	0.045	
KCNK3	HapB2					0.345	0.842	
KCNK3	HapB4					0.182	0.913	
KCNK9	rs2542424	140701683	8	0.362	A > G	0.342	0.843	A
KCNK9	rs2542422	140706306	8	0.328	C > A	1.009	0.604	A
KCNK9	rs2014712	140709816	8	0.235	C > T	1.458	0.482	A
KCNK9	rs2545462	140714686	8	0.343	C > A	2.62	0.27	A
KCNK9	rs2542420	140714883	8	0.419	C > G	3.723	0.155	A
KCNK9	rs2545461	140717431	8	0.257	A > G	NA	NA	NA
KCNK9	rs3780051	140727983	8	0.471	A > G	FE	0.022	R
KCNK9	rs2545457	140730467	8	0.35	T > C	FE	0.046	D
KCNK9	rs2005895	140738217	8	0.256	T > C	2.1	0.35	A
KCNK9	rs888349	140738927	8	0.197	A > C	0.158	0.924	A
KCNK9	rs759656	140739149	8	0.32	T > C	NA	NA	NA

Continued on the next page

SUPPLEMENTAL TABLE 1. Summary of SNPs Analyzed for Potassium Channel Genes Between the High and Low–Moderate Attentional Function Classes *(Continued)*

Gene	SNP	Position	Chr	MAF	Alleles	χ^2	p	Model
2-pore domain potassium channels *(continued)*								
KCNK9	rs13277242	140739269	8	0.495	G > A	2.878	0.237	A
KCNK9	rs885724	140740112	8	0.38	A > C	0.545	0.762	A
KCNK9	rs3780039	140745846	8	0.372	T > G	1.298	0.523	A
KCNK9	rs10110946	140754803	8	0.333	T > C	0.11	0.946	A
KCNK9	rs7828107	140756023	8	0.409	C > A	0.534	0.766	A
KCNK9	rs983740	140762922	8	0.472	T > G	2.811	0.245	A
KCNK9	rs11166921	140776937	8	0.395	C > A	2.035	0.361	A
KCNK9	rs13278664	140779544	8	0.455	A > G	0.388	0.824	A
KCNK9	HapA1					2.924	0.232	
KCNK9	HapA2					1.196	0.55	
KCNK9	HapA3					0.257	0.879	
KCNK9	HapB1					4.766	0.092	
KCNK9	HapB4					1.649	0.438	
KCNK9	HapC1					0.109	0.947	
KCNK9	HapC3					1.981	0.371	
KCNK9	HapC4					0.566	0.754	
KCNK9	HapD1					2.496	0.287	
KCNK9	HapD2					0.362	0.834	
KCNK9	HapD3					1.854	0.396	

A—additive model; chr—chromosome; D—dominant model; hap—haplotype; *KCNA1*—voltage-gated potassium channel subfamily A member 1; *KCND2*—voltage-gated potassium channel subfamily D member 2; *KCNJ3*—inwardly rectifying potassium channel subfamily J member 3; *KCNJ5*—inwardly rectifying potassium channel subfamily J member 5; *KCNJ9*—inwardly rectifying potassium channel subfamily J member 9; *KCNJ6*—inwardly rectifying potassium channel subfamily J member 6; *KCNK9*—2-pore domain potassium channel subfamily K member 9; *KCNK3*—2-pore domain potassium channel subfamily K member 3; *KCNS1*—voltage-gated potassium channel modifier subfamily S member 1; *KCNK2*—2-pore domain potassium channel subfamily K member 2; MAF—minor allele frequency; NA—not applicable; R—recessive model; SNP—single nucleotide polymorphism
Note. NA values were not assayed because the SNP violated Hardy–Weinberg expectations ($p < 0.001$) or because the MAF was less than 0.05.