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VARIATIONS IN POTASSIUM CHANNEL GENES ARE ASSOCIATED WITH BREAST PAIN IN WOMEN PRIOR TO BREAST CANCER SURGERY

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Abstract

Preoperative breast pain in women with breast cancer may result from a number of causes. Previous work from our team found that breast pain occurred in 28.2% of women (n=398) who were about to undergo breast cancer surgery. The occurrence of preoperative breast pain was associated with a number of demographic and clinical characteristics, as well as variation in two cytokine genes. Given that ion channels regulate excitability of sensory neurons, we hypothesized that variations in potassium channel genes would be associated with preoperative breast pain in these patients. Therefore, in this study we evaluated for associations between single nucleotide polymorphisms and inferred haplotypes among 10 potassium channel genes and the occurrence of preoperative breast pain in patients scheduled to undergo breast cancer surgery. Multivariable logistic regression analyses were used to identify those genetic variations that were associated with the occurrence of preoperative breast pain while controlling for age and genomic estimates of and self-reported race/ethnicity. Variations in four potassium channel genes: 1) potassium voltage-gated channel, delayed rectifier, subfamily S, member 1 (KCNS1); 2) potassium inwardly-rectifying channel, subfamily J, member 3 (KCNJ3); 3) KCNJ6; and 4) potassium channel, subfamily K, member 9 (KCNK9) were associated with the occurrence of breast pain. Findings from this study warrant replication in an independent sample of women who report breast pain following one or more breast biopsies.

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Keywords

breast pain; preoperative pain; potassium channel genes; breast cancer; candidate genes

INTRODUCTION

Breast pain prior to breast cancer surgery was noted by surgeons several decades ago (Corry, 1952; Lane-Claypon, 1926). Prevalence estimates for preoperative breast pain range from 14% to 53% (Corry, 1952; Poleshuck et al., 2006; Tasmuth, von Smitten, & Kalso, 1996). Before the advent of screening mammography and diagnostic biopsies, this localized pain was considered a somewhat reliable indicator of malignant disease (Corry, 1952). This preoperative pain was described as aching or stabbing (Corry, 1952) and reported to interfere with daily activities (Tasmuth, et al., 1996). Aside from these observations, very little information is available on the characteristics of and mechanisms that underlie this clinical condition.

In an attempt to address this gap, our group recently reported on the occurrence of preoperative breast pain as well as its severity, qualities, and impact on function (McCann et al., 2012). Consistent with published reports, 28% of women reported pain in the breast prior to surgery. Average and worst pain scores were 2.2 and 3.6, respectively, using a 0 to 10 numeric rating scale (NRS). This pain significantly interfered with activities of daily living an average of 6.2 hours per day for approximately 3 days a week. Using the Pain Qualities Assessment Scale (PQAS) (Jensen et al., 2006), the qualities with the highest ratings were tender, dull, and aching. In addition, preoperative breast pain interfered with patients' sleep and mood. Compared to women without preoperative breast pain, women with pain were younger; more likely to be non-white; less likely to be post-menopausal; had lower functional status scores; and more breast biopsies in the past year (McCann et al., 2012). In addition, preoperative breast pain was associated with higher depressive symptom scores and poorer physical well-being (Kyranou et al., 2012). Moreover, women who reported preoperative breast pain were significantly more likely to report persistent pain for six months following breast cancer surgery (Miaskowski et al., 2012b).

We hypothesized that this preoperative breast pain would have an inflammatory component. Consistent with this hypothesis, the rare allele of a single nucleotide polymorphism (SNP) in interleukin (IL) receptor 2 (IL1R2; rs2110726) was associated with decreased risk for preoperative pain and the rare allele of a SNP in IL13 (rs1295686) was associated with increased risk for preoperative pain (McCann et al., 2012). However, given that pain is a complex trait, other genetic factors may contribute to the variability in the occurrence of preoperative breast pain.

This preoperative breast pain may be due to altered neuronal excitability. Potassium channels, the most ubiquitous type of ion channel (Miller, 2000), are distributed centrally and peripherally, and play a key role in the maintenance of resting membrane potential, the regulation of neuronal excitability (Dodson & Forsythe, 2004; Wickenden, 2002), and the transmission of nociceptive information to the central nervous system (Xie, 2007). Variations in a number of potassium channel genes are associated with thermal hyperalgesia

(Alloui et al., 2006; Marker, Stoffel, & Wickman, 2004) and inflammatory pain (Marsh et al., 2012) in rodents, analgesic responses in mice and humans (Blednov et al., 2003; Marker et al., 2004; Nishizawa et al., 2009), and a number of chronic pain conditions in humans (Costigan et al., 2010).

Given their involvement in pain and analgesia, we hypothesized that variations in potassium channel genes would be associated with the occurrence of preoperative breast pain in women prior to breast cancer surgery. Specifically, we evaluated for associations between variations in 10 potassium channel genes and the occurrence of preoperative breast pain in a sample of patients scheduled to undergo breast cancer surgery. These candidate genes encode for three classes of potassium channels (KCN): voltage-gated potassium channels (i.e., KCNA1, KCND2, KCNS1), inward-rectifying potassium channels (i.e., KCNJ3, KCNJ5, KCNJ6, KCNJ9), and two-pore domain potassium channels (i.e., KCNK2, KCNK3, KCNK9).

METHODS

Patients and Settings

This analysis is part of a larger study of women undergoing breast cancer surgery (McCann et al., 2012; Miaskowski et al., 2012b; Miaskowski et al., 2013). Patients were recruited from seven breast care centers in the San Francisco Bay Area.

Eligible patients were adult women (>18 years) scheduled to undergo breast cancer surgery on one breast; were able to read, write, and understand English; and gave written informed consent. Exclusion criteria included having breast cancer surgery on both breasts and/or distant metastasis at the time of diagnosis. Of the 516 patients who were approached to participate, 410 were enrolled (response rate 79.4%), and 398 completed the baseline assessment.

Instruments

A demographic questionnaire obtained information on age, marital status, education, ethnicity, employment status, and living arrangements. The Karnofsky Performance Status (KPS) scale was used to evaluate functional status (Karnofsky et al., 1948). For this study, the KPS scale ranged from 30 (I feel severely disabled and need to be hospitalized) to 100 (I feel normal; I have no complaints or symptoms). The KPS scale has well established validity and reliability (Karnofsky, 1977).

The Self-Administered Comorbidity Questionnaire (SCQ) was used to measure the occurrence, severity, and functional limitations of 13 common medical conditions (Sangha et al., 2003). The SCQ has well-established validity and reliability and has been used in studies of patients with a variety of chronic conditions (Brunner et al., 2008; Sangha et al., 2003).

At the time of enrollment, patients were asked whether they currently had pain in their affected breast (yes/no). Responses to this question were used to dichotomize the sample into patients with (n=110) and without (n=280) breast pain prior to surgery.

Study Procedures

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 the patient's preoperative visit, a clinician explained the study and determined the patient's willingness to participate. Women who were willing to participate met with the research nurse who determined eligibility and obtained written informed consent prior to surgery. Patients completed the enrollment questionnaires on average four days prior to surgery. Medical records were reviewed for disease and treatment information.

Genomic Analyses

Gene selection—Candidate genes were selected based on evidence in the literature of an association between the gene and various pain outcomes (e.g., pain severity). In addition to a literature search of potassium channel genes and pain in humans, the Pain Genes Database (Lacroix-Fralish, Ledoux, & Mogil, 2007) was used to identify potassium channel genes. In total, 10 potassium channel genes were selected. Three of the selected genes encode for voltage-gated potassium channels (i.e., KCNA1, KCND2, KCNS1); four encode for inward-rectifying potassium channels (i.e., KCNJ3, KCNJ5, KCNJ6, KCNJ9); and three encode for two-pore domain potassium channels (i.e., KCNK2, KCNK3, KCNK9).

Blood collection and genotyping—Of the 398 patients who completed the baseline questionnaires, 302 provided a blood sample. Genomic DNA was extracted from PBMCs using the PUREGene DNA Isolation System (Invitrogen, Carlsbad, CA). Samples were genotyped using the Golden Gate genotyping platform (Illumina, San Diego, CA) and processed using GenomeStudio (Illumina, San Diego, CA). Genotyping was performed blinded to pain group status and positive and negative controls were included.

SNP Selection—A combination of tag-SNPs and literature driven SNPs were selected for analysis. Tag-SNPs were common (minor allele frequency ≥0.05) in public databases. SNPs with call rates <95% or Hardy-Weinberg p<.001 were excluded. As shown in Table 1, a total of 155 SNPs among the 10 candidate genes (KCNA1: 1 SNP; KCND2: 9 SNPs; KCNS1: 4 SNPs; KCNJ3: 28 SNPs; KCNJ5: 8 SNPs; KCNJ6: 58 SNPs; KCNJ9: 2 SNPs; KCNK2: 22 SNPs, KCNK3: 6 SNPs; KCNK9: 17 SNPs) passed all quality control filters and were included in the genetic association analyses. Potential functional roles for SNPs associated with preoperative breast pain were examined using PUPASuite 3.1 (Conde et al., 2006).

Statistical Analyses for the Phenotypic Data

Data were analyzed using SPSS version 19 (SPSS, 2010) and STATA Version 12 (StataCorp, 2005). Independent samples t-tests, Mann-Whitney U tests, and Chi-square analyses were used to evaluate for differences in demographic and clinical characteristics between the pain and no pain groups. All calculations used actual values. Adjustments were not made for missing data.

Statistical Analyses for the Genetic Data

Allele and genotype frequencies were determined by gene counting. Hardy-Weinberg equilibrium was assessed by the Chi-square or Fisher Exact tests. Measures of linkage disequilibrium ((LD); i.e., D' and r^2) were computed from the patients' genotypes using Haploview 4.2. LD-based haplotype block definition was based on D' confidence interval (Gabriel et al., 2002).

Haplotype analyses were conducted in order to localize the association signal within each gene and to determine if haplotypes improved the strength of the association with the phenotype. Haplotypes were constructed using the PHASE version 2.1 (Stephens, Smith, & Donnelly, 2001). Only haplotypes that were inferred with probability estimates of >.85, across five iterations, were retained for subsequent analyses.

One hundred and six ancestry informative markers (AIMs) were used to control for population stratification (i.e., race/ethnicity) (Halder et al., 2008; Hoggart et al., 2003; Tian, Gregersen, & Seldin, 2008). Using Helix Tree (Golden Helix, Bozeman, MT), homogeneity in ancestry among patients was verified by principal component (PC) analysis (Price et al., 2006) (data not shown). The first three PCs were selected to adjust for potential confounding due to population substructure by including the three covariates in all regression models.

For association tests, additive, dominant, and recessive genetic models were assessed for each SNP. Barring small improvements from the additive model (i.e., delta <10%), the model that best fit the data (by maximizing the significance of the p-value) was selected for each SNP. Logistic regression analysis that controlled for significant covariates, genomic estimates of and self-reported race/ethnicity, and variation in other SNPs/haplotypes within the same gene, was used to evaluate the association between genotype and pain group membership. A backwards stepwise approach was used to create a parsimonious model. Genetic model fit and covariate-adjusted odds ratios were estimated using STATA version 12.

As done previously (Dunn et al., 2013; Illi et al., 2012; McCann et al., 2012; Miaskowski et al., 2012a), based on recommendations in the literature (Hattersley & McCarthy, 2005; Rothman, 1990) as well as the implementation of rigorous quality controls, the non-independence of genetic markers in LD, and the exploratory nature of the analyses, adjustments were not made for multiple testing. Moreover, significant SNPs identified in the bivariate analyses were evaluated using regression analyses that controlled for differences in phenotypic characteristics, potential confounding due to population stratification, and variation in other SNPs/haplotypes within the same gene. Only those SNPs that remained statistically significant in the multivariable analyses were included in the final presentation of the results. Therefore, the identified significant genetic associations are unlikely to be due solely to chance. Unadjusted associations are reported for all SNPs passing quality control criteria in Table 1 to allow for subsequent comparisons and meta-analyses.

RESULTS

Differences in Demographic and Clinical Characteristics

A detailed description of the differences in demographic and clinical characteristics between our patients with and without preoperative breast pain is available elsewhere (McCann et al., 2012). Table 2 summarizes only those characteristics that differed significantly between the two groups. The characteristics associated with the occurrence of preoperative breast pain were younger age, lower functional status, being non-white, being pre-menopausal, and having more biopsies in the past year.

Regression Analyses for KCNJ3, KCNJ6, KCNK9, and KCNS1 Genotypes and Haplotypes

In order to better estimate the magnitude (i.e., odds ratio, OR) and precision (95% confidence interval [CI]) of genotype on the odds of reporting preoperative breast pain, multivariate logistic regression models were fit. Using a backwards stepwise approach, age was the only phenotypic characteristic listed in Table 2 that remained significant in this initial logistic regression model. Age was included as a covariate in subsequent models that evaluated genotypic predictors. Each 5-year increase in age was associated with a 23% reduction in odds of reporting preoperative breast pain (OR: 0.77; 95% CI: 0.682, 0.878).

After controlling for age and genomic estimates of and self-reported race/ethnicity, and variation in other SNPs/haplotypes within the same gene, eight genetic associations (7 SNPs, 1 haplotype) among four candidate genes were associated with pain group membership: KCNS1 (rs4499491); KCNJ3 (rs7574878) and haplotype E1 (composed of rs2591168 and rs2591172); KCNJ6 (rs2835914, rs8129919, rs2836050); and KCNK9 (rs3780039, rs11166921; see Table 3).

For KCNS1 rs4499491, individuals homozygous for the rare A allele (CC+CA versus AA) had a 3.0-fold increase in the odds of reporting preoperative breast pain.

For KCNJ3 rs7574878, individuals who were heterozygous or homozygous for the rare G allele (TT versus TG+GG) had a 48% reduction in the odds of reporting preoperative breast pain. In addition, each dose of the KCNJ3 haplotype E1 (composed of the common A allele at rs2591168 and the rare G allele at rs2591172; Figure 1) was associated with a 1.7-fold increase in the odds of reporting preoperative breast pain.

For KCNJ6, three SNPs (i.e., rs2835914, rs8129919, rs2836050) were associated with the occurrence of preoperative breast pain. For KCNJ6 rs2835914, individuals who were heterozygous or homozygous for the rare C allele (GG versus GC+CC) had a 52% reduction in the odds of reporting preoperative breast pain. For KCNJ6 rs8129919, each dose of the rare A allele (GG versus GA versus AA) was associated with a 2.1-fold increase in the odds of reporting preoperative breast pain. For KCNJ6 rs2836050, individuals homozygous for the rare T allele (CC+CT versus TT) had a 3.6-fold increase in the odds of reporting preoperative breast pain.

For KCNK9, two SNPs (i.e., rs3780039, rs11166921) were associated with the occurrence of preoperative breast pain. For KCNK9 rs3780039, individuals who were heterozygous or

homozygous for the rare G allele (TT versus TG+GG) had a 1.9-fold increase in the odds of reporting preoperative breast pain. For KCNK9 rs11166921, individuals homozygous for the rare A allele (CC+CA versus AA) had a 2.4-fold increase in the odds of reporting preoperative breast pain.

DISCUSSION

This study provides new evidence of associations between four potassium channel genes and the occurrence of breast pain prior to breast cancer surgery. These findings build on our previous work that identified associations between cytokine gene variations and preoperative breast pain (McCann et al., 2012). While our initial phenotypic and genotypic findings suggested that preoperative breast pain has an inflammatory component, the current findings suggest that potassium channel activity also contributes to preoperative breast pain. These findings are not discrepant, because interplay may exist between potassium channels and cytokines that presents an interesting avenue for future research.

Differences in demographic and clinical characteristics between women with and without breast pain prior to breast cancer surgery are discussed in detail elsewhere (McCann et al., 2012). However, it is interesting to note that age was the only phenotypic characteristic that remained significant in the final phenotypic regression model. Each 5-year increase in age was associated with a 23% reduction in the odds of reporting breast pain. This finding is consistent with previous reports of age-related differences in the occurrence of cancer pain (Gibson & Helme, 2001). In addition, it is consistent with work from our research group that found decreases in the occurrence rates for a number of common symptoms (e.g., depressive symptoms, fatigue, sleep disturbance) in older oncology patients (Dunn et al., 2012; Dunn et al., 2013; Illi et al., 2012; Linden et al., 2012). The effect of age on the occurrence of preoperative breast pain warrants additional investigation, as some reviews noted that a number of persistent pain conditions increase with age (Fillingim, 2005; Gibson & Helme, 2001).

Of the three voltage-gated potassium channel genes that were evaluated, only KCNS1, which encodes for the potassium channel, Kv9.1, demonstrated an association with the occurrence of preoperative breast pain. In this sample, patients who were homozygous for the rare “A” allele for KCNS1 rs4499491, located in the 3′ untranslated region of KCNS1, had a 3-fold increase in the odds of reporting preoperative breast pain. While no functional data are reported for this SNP, it is located in a conserved region of the gene. Therefore, it may be functional or may be in LD with an unmeasured functional SNPs. Interestingly, the minor allele of a nearby functional SNP rs734784 (isoleucine to valine missense mutation) was associated with an increased risk for a number of persistent pain conditions (Costigan et al., 2010). However, rs734784 was not associated with ratings of average pain in women at least one year after surgery for breast cancer (Costigan et al.). The estimates of LD between rs4499491 and rs734784 (D’ = 0.416, r^2 = 0.106) in our study suggest that the association observed between rs4199491 and preoperative pain is not likely to be attributable to its LD with rs734784. Moreover, no association was found between KCNS1 rs734784 and preoperative pain in our study.

Located on sensory neurons, voltage-gated potassium channels play a key role in modulating resting membrane potentials as well as the shape and magnitude of action potentials (Takeda et al., 2011; Tsantoulas et al., 2012). Although non-functional on its own, Kv9.1 modifies the activity of co-expressed functional voltage-gated potassium channels. (Richardson & Kaczmarek, 2000). Taken together, these findings suggest that KCNS1 may play a role in the pathophysiology of pain. The specific SNP identified in this study (i.e., rs4499491) warrants additional investigation in terms of its role in preoperative pain as well as persistent postsurgical pain.

Four genes that encode for G-protein-gated inwardly-rectifying potassium (GIRK) channels were evaluated in our study. Only KCNJ3 (GIRK1) and KCNJ6 (GIRK2) were associated with the occurrence of preoperative breast pain. All four of the polymorphisms identified are intronic. However, with the exception of one SNP in haplotype E1, they are located in conserved regions of the gene. Therefore, they may be functional or in LD with nearby functional SNPs.

GIRK channels are involved in postsynaptic inhibition in response to a number of neurotransmitters (Luscher & Slesinger, 2010), including those implicated in pain transmission (e.g., dopamine, serotonin, gamma-aminobutyric acid, opioids) (Fields, Heinricher, & Mason, 1991; Luscher & Slesinger, 2010). In addition, GIRK1 and GIRK2 channels closely interact with opioid receptors to modulate neuronal transmission (Ulens, Daenens, & Tytgat, 1999). Evidence from animal models suggests that GIRK1 (KCNJ3) and GIRK2 (KCNJ6), but not GIRK3 (KCNJ9), subunits are expressed in the superficial layers of the dorsal horn; play a role in thermal nociception and analgesic responses to morphine; and are highly interactive (Marker et al., 2004). Consistent with findings of altered thermal nociception in transgenic mice (Marker et al., 2004), only variations in KCNJ3 and KCNJ6, but not KCNJ9, were associated with the occurrence of preoperative breast pain in our sample. Given the substantial evidence for the role of these channels in the modulation of nociceptive transmission, additional investigations are warranted on the role of GIRK channels in preoperative breast pain.

Of the three two-pore domain potassium leak channel genes evaluated in this study, only variations in KCNK9 (TWIK-related acid sensing potassium channel-3; TASK3) were associated with an increased risk for the occurrence of preoperative breast pain. While these two intronic SNPs have no known function, they are located in a conserved region of KCNK9 and may be in LD with an unmeasured functional SNPs.

Two-pore domain potassium leak channels establish resting membrane potentials, play a key role in the modulation of neuronal excitability (Lesage, 2003; Talley et al., 2003), and are expressed in sensory neurons of rat DRG (Rau, Cooper, & Johnson, 2006). Like GIRK channels, TASK channels are inhibited by several neurotransmitters (Talley et al., 2000). Recently, in a rodent model of cutaneous inflammation, TASK3 mRNA expression in DRG neurons was reduced bilaterally four days after unilateral inflammation compared to one day after inflammation (Marsh et al., 2012). In addition, reduced mRNA expression was associated with reduced ipsilateral spontaneous pain behavior (i.e., foot lifting) (Marsh, et al., 2012). Further investigation of KCNK9, including an evaluation of whether genetic

variations (e.g., rs3780039, rs11166921) are associated with TASK3 expression levels, is warranted.

In light of our previous findings (McCann et al., 2012), which suggested that preoperative breast pain has an inflammatory component, it is possible that gene × gene interactions between cytokine and potassium channel genes may occur and result in a higher risk for preoperative breast pain. This hypothesis is supported by work that demonstrates that potassium channel activity can impact cytokine production in lymphocytes (Feske, Skolnik, & Prakriya, 2012) and THP-1 cells through toll-like receptor 4 inhibition (Jo et al., 2011). Larger samples are needed to test for such potential epistatic interactions in patients with preoperative breast pain.

Some study limitations should be noted. Firstly, in this study, preoperative breast pain was operationalized as pain occurring in the affected breast prior to breast cancer surgery. Because the timeframe of occurrence was not evaluated, it is not clear whether this preoperative breast pain was acute or chronic in nature. Secondly, as with any association study, it is important to note that the genetic associations identified herein are not necessarily causal. Replication in independent samples, followed by functional studies and/or deep sequencing may be required before a causal relationship between these SNPs and the occurrence of preoperative breast pain is established. Thirdly, with an increased sample size, additional genetic associations may be identified. Likewise, regression models would have sufficient power to fit interaction terms (e.g., gene × environment interactions). Finally, although our sample size of 302 is substantial, it is possible that these associations may not be replicated in an independent sample (Ioannidis et al., 2001).

In summary, this study identified eight genetic variations among four potassium channel genes (i.e., KCNS1, KCNJ3, KCNJ6, KCNK9) that were significantly associated with the occurrence of preoperative breast pain. Variation among these genes may constitute important risk factors for the occurrence of preoperative breast pain. Moreover, in our work preoperative breast pain was associated with more severe postoperative pain data in preparation), as well as with the development of persistent breast pain after breast cancer surgery (Miaskowski et al., 2012b). An evaluation of genetic associations may help to identify the underlying mechanisms for preoperative, postoperative, and persistent pain in patients who undergo breast cancer surgery.

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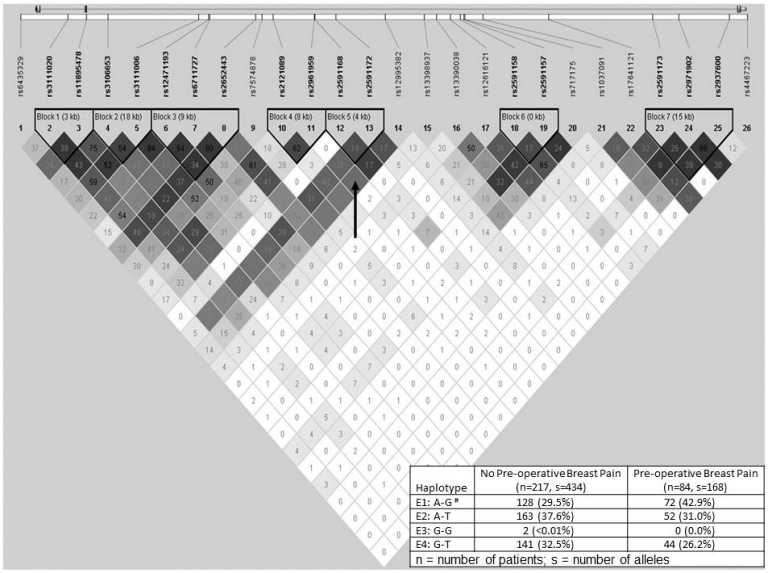

Figure 1.

KCNJ3 linkage disequilibrium-based heatmap and haplotype analysis. An ideogram of potassium inwardly-rectifying channel, subfamily J, member 3 (KCNJ3, GIRK1, Kir3.1) is presented above the white bar that represents the physical distance along human (chromosome 2 position 155555093 to 155714864; genome build 37.10, NC_000002.11). Exons are represented as boxes. Gray lines connecting the exons represent introns. The direction of transcription is from left to right. Reference sequence identifiers (rsID) for each single nucleotide polymorphism (SNP) are plotted both in terms of their physical distance (i.e., the white bar at the top of the figure) and equidistantly in order to render the pairwise linkage disequilibrium (LD) estimates that were calculated and visualized with Haploview 4.2. The gene structure for KCNJ3 (i.e., hg18 NM_002239) was rendered with FancyGene 1.4. The correlation statistics (r^2 and D') are provided in the heatmap. LD-based haplotype block definition was based on D' confidence interval (Conde et al., 2006a). The haploblock is outlined in a bolded triangle and its component SNPs are rendered in bold font. Pairwise D' values (range: 0-1, inclusive) were rendered in greyscale, with dark grey diamonds representing D' values approaching 1.0. When the r^2 values (range of 0-100, inclusive) are not equal to 0 or 100, they are provided in a given diamond. The haplotypes i.e., HapE1-HapE4) observed in the haploblock 5 (i.e., "Block 5" indicated by the vertical black arrow in the figure) are listed in each row, starting with the nucleotide composition across the two SNPs that compose the haplotype (i.e., rs2591168, rs2591172) and the count frequency (%) of each haplotype observed in the no preoperative breast pain and preoperative breast pain groups.

#The haplotype E1, composed of the "A" common allele at rs2591168 and the "G" rare allele at rs2591172, identified in the bivariate analyses (Table 1) remained significant after controlling for relevant covariates.

Table 1

Summary of Potassium Channel Gene Single Nucleotide Polymorphisms (SNPs) and Haplotypes Analyzed for Pain Versus No Pain in Women Prior to Breast Cancer Surgery

Gene	SNP	Position	Chr	MAF	Alleles	Chi Square	p-value	Model
VOLTAGE-GATED POTASSIUM CHANNELS								
KCNA1	rs4766311	4892699	1	0.466	C>T	3.16	0.206	A
KCND2	rs17376373	119787721	7	0.197	T>G	4.36	0.113	A
KCND2	rs702414	119924204	7	0.249	G>C	3.52	0.172	A
KCND2	rs802340	119975021	7	0.293	G>T	1.87	0.393	A
KCND2	rs12706292	120012310	7	0.346	A>G	0.08	0.963	A
KCND2	rs4730967	120060462	7	0.320	T>C	4.52	0.104	A
KCND2	rs1072198	120114585	7	0.304	A>G	0.63	0.730	A
KCND2	rs11489533	120117902	7	0.268	A>G	0.70	0.704	A
KCND2	rs4727914	120122574	7	0.343	A>G	4.40	0.111	A
KCND2	rs12673992	120160059	7	0.319	A>G	0.01	0.996	A
KCND2	HapA1					0.77	0.682	
KCND2	HapA3					4.40	0.111	
KCNS1	rs4499491	43154833	20	0.432	C>A	FE	0.001	R
KCNS1	rs6124684	43154907	20	0.223	C>T	FE	0.025	D
KCNS1	rs734784	43157041	20	0.447	A>G	4.31	0.116	A
KCNS1	rs6073643	43161484	20	0.274	T>C	1.31	0.520	A
KCNS1	HapA1					12.71	0.002	
KCNS1	HapA2					3.96	0.138	
KCNS1	HapA3					5.36	0.069	
KCNS1	HapB1					4.31	0.116	
KCNS1	HapB2					5.43	0.066	
KCNS1	HapB3					1.38	0.501	
INWARD-RECTIFYING POTASSIUM CHANNELS								
KCNJ3	rs6435329	155265893	2	0.445	G>T	FE	0.014	D
KCNJ3	rs3111020	155275635	2	0.450	T>C	FE	0.025	D
KCNJ3	rs11895478	155279369	2	0.246	C>T	FE	0.027	D
KCNJ3	rs3106653	155283806	2	0.262	A>C	FE	0.014	D
KCNJ3	rs3111003	155300413	2	0.465	C>T	2.45	0.294	A
KCNJ3	rs3111006	155302345	2	0.375	C>T	4.59	0.101	A
KCNJ3	rs12471193	155304383	2	0.343	A>G	4.83	0.089	A
KCNJ3	rs6711727	155304684	2	0.485	G>A	1.29	0.524	A
KCNJ3	rs2652443	155313983	2	0.395	G>A	5.49	0.064	A
KCNJ3	rs7574878	155315394	2	0.429	T>G	FE	<.0001	D
KCNJ3	rs2121085	155315711	2	0.447	A>G	9.04	0.011	A

Gene	SNP	Position	Chr	MAF	Alleles	Chi Square	p-value	Model
KCNJ3	rs2121089	155317633	2	0.479	C>A	FE	0.041	D
KCNJ3	rs2961959	155326068	2	0.432	C>G	FE	0.045	R
KCNJ3	rs2591168	155326179	2	0.316	A>G	2.37	0.306	A
KCNJ3	rs2591172	155330423	2	0.333	T>G	9.29	0.010	A
KCNJ3	rs12995382	155340539	2	0.290	T>C	1.40	0.498	A
KCNJ3	rs13398937	155348593	2	0.362	C>G	2.16	0.339	A
KCNJ3	rs13390038	155351011	2	0.403	G>A	2.96	0.228	A
KCNJ3	rs12616121	155353928	2	0.469	A>G	2.00	0.367	A
KCNJ3	rs2591158	155355912	2	0.280	A>C	1.42	0.491	A
KCNJ3	rs2591157	155356612	2	0.330	A>G	1.25	0.536	A
KCNJ3	rs717175	155356841	2	0.332	C>T	5.27	0.072	A
KCNJ3	rs1037091	155360603	2	0.375	G>A	2.63	0.269	A
KCNJ3	rs17641121	155373998	2	0.259	T>C	0.39	0.824	A
KCNJ3	rs2591173	155395322	2	0.477	C>A	2.53	0.283	A
KCNJ3	rs2971902	155400624	2	0.220	G>T	0.87	0.649	A
KCNJ3	rs2937600	155411014	2	0.299	A>G	0.34	0.843	A
KCNJ3	rs4467223	155414657	2	0.479	T>A	0.28	0.871	A
KCNJ3	HapA1					0.20	0.907	
KCNJ3	HapA2					5.64	0.060	
KCNJ3	HapA3					6.08	0.048	
KCNJ3	HapB1					6.43	0.040	
KCNJ3	HapB4					5.75	0.056	
KCNJ3	HapC3					5.46	0.065	
KCNJ3	HapC5					5.87	0.053	
KCNJ3	HapD1					5.95	0.051	
KCNJ3	HapD4					5.69	0.058	
KCNJ3	HapE1					10.55	0.005	
KCNJ3	HapE2					3.69	0.158	
KCNJ3	HapE4					2.06	0.358	
KCNJ3	HapF1					1.49	0.475	
KCNJ3	HapF2					0.31	0.858	
KCNJ3	HapF4					1.35	0.509	
KCNJ3	HapG1					0.89	0.642	
KCNJ3	HapG3					0.87	0.649	
KCNJ3	HapG4					2.46	0.293	
KCNJ5	rs7941582	128266885	11	0.408	A>G	1.87	0.393	A
KCNJ5	rs2846700	128274148	11	0.172	A>G	1.51	0.469	A
KCNJ5	rs4937384	128285012	11	0.223	T>C	2.47	0.290	A
KCNJ5	rs11221503	128277662	11	0.184	C>T	0.45	0.800	A

Gene	SNP	Position	Chr	MAF	Alleles	Chi Square	p-value	Model
KCNJ5	rs2604212	128278165	11	0.459	C>G	0.17	0.920	A
KCNJ5	rs4937387	128278623	11	0.257	T>C	0.29	0.865	A
KCNJ5	rs11221510	128285907	11	0.241	A>T	0.27	0.876	A
KCNJ5	rs6590357	128286549	11	0.163	C>T	0.03	0.987	A
KCNJ5	HapA1					0.38	0.826	
KCNJ5	HapA2					0.17	0.920	
KCNJ5	HapA5					0.33	0.846	
KCNJ6	rs860795	37937160	21	0.208	G>C	0.25	0.884	A
KCNJ6	rs1709838	37941983	21	0.431	C>A	0.68	0.710	A
KCNJ6	rs10483038	37946641	21	0.279	T>C	0.36	0.835	A
KCNJ6	rs857967	37954006	21	0.197	T>A	3.41	0.182	A
KCNJ6	rs2835885	37961436	21	0.432	T>G	0.67	0.714	A
KCNJ6	rs858010	37987109	21	0.166	G>A	0.03	0.983	A
KCNJ6	rs1005546	37990742	21	0.450	C>T	0.51	0.777	A
KCNJ6	rs858003	37994854	21	0.197	C>T	1.76	0.416	A
KCNJ6	rs1709816	37999129	21	0.390	G>T	1.20	0.548	A
KCNJ6	rs13049947	38002710	21	0.403	C>T	0.26	0.877	A
KCNJ6	rs2835914	38020720	21	0.347	G>C	FE	0.027	D
KCNJ6	rs858035	38021061	21	0.344	T>C	FE	0.010	D
KCNJ6	rs13048511	38037731	21	0.468	A>G	1.82	0.403	A
KCNJ6	rs2835925	38041173	21	0.176	A>G	1.40	0.497	A
KCNJ6	rs857989	38042001	21	0.115	G>C	0.20	0.906	A
KCNJ6	rs2835931	38043518	21	0.282	C>T	1.51	0.469	A
KCNJ6	rs1399596	38045382	21	0.260	T>C	2.44	0.295	A
KCNJ6	rs2835942	38052778	21	0.303	C>T	3.44	0.179	A
KCNJ6	rs2835945	38057170	21	0.398	G>A	2.43	0.297	A
KCNJ6	rs1160350	38065897	21	0.494	G>C	4.31	0.116	A
KCNJ6	rs762145	38068188	21	0.366	C>T	1.14	0.566	A
KCNJ6	rs2226356	38075902	21	0.427	C>T	1.25	0.535	A
KCNJ6	rs1787337	38077824	21	0.494	A>G	2.59	0.274	A
KCNJ6	rs2835961	38083028	21	0.482	G>A	2.62	0.269	A
KCNJ6	rs2835976	38103779	21	0.385	C>T	0.47	0.790	A
KCNJ6	rs2835977	38104067	21	0.224	G>A	0.07	0.967	A
KCNJ6	rs2211842	38105403	21	0.376	C>A	0.33	0.846	A
KCNJ6	rs2211843	38106055	21	0.234	G>T	1.78	0.410	A
KCNJ6	rs2211845	38106371	21	0.447	T>C	1.20	0.549	A
KCNJ6	rs2835982	38110247	21	0.368	C>A	0.84	0.658	A
KCNJ6	rs2835983	38110476	21	0.304	G>A	1.30	0.521	A
KCNJ6	rs2835984	38110657	21	0.497	A>T	0.40	0.818	A

Gene	SNP	Position	Chr	MAF	Alleles	Chi Square	p-value	Model
KCNJ6	rs3787835	38111440	21	0.455	C>T	1.28	0.527	A
KCNJ6	rs6517435	38117092	21	0.422	G>A	0.30	0.859	A
KCNJ6	rs2154556	38120757	21	0.344	T>C	1.55	0.462	A
KCNJ6	rs4817896	38123831	21	0.248	C>T	0.23	0.892	A
KCNJ6	rs3787840	38124263	21	0.139	C>T	1.17	0.558	A
KCNJ6	rs991985	38128024	21	0.286	C>A	0.04	0.979	A
KCNJ6	rs2836007	38128761	21	0.194	C>T	0.11	0.947	A
KCNJ6	rs2836013	38132582	21	0.292	C>T	0.39	0.823	A
KCNJ6	rs2836016	38134890	21	0.411	A>G	0.49	0.785	A
KCNJ6	rs2836019	38136864	21	0.327	C>T	2.04	0.360	A
KCNJ6	rs915800	38138203	21	0.455	C>T	1.18	0.554	A
KCNJ6	rs2226741	38146803	21	0.147	A>G	1.40	0.496	A
KCNJ6	rs7276928	38147607	21	0.288	G>A	2.00	0.368	A
KCNJ6	rs3827199	38149472	21	0.408	G>A	3.27	0.195	A
KCNJ6	rs4816585	38151120	21	0.495	G>A	1.26	0.533	A
KCNJ6	rs9305628	38166861	21	0.227	A>G	FE	0.036	D
KCNJ6	rs9974219	38168568	21	0.277	A>T	4.10	0.129	A
KCNJ6	rs7277957	38168770	21	0.492	A>G	1.50	0.473	A
KCNJ6	rs1892682	38169935	21	0.265	G>A	0.61	0.738	A
KCNJ6	rs928765	38173472	21	0.292	C>T	1.77	0.413	A
KCNJ6	rs3787862	38174571	21	0.197	G>A	0.74	0.692	A
KCNJ6	rs10775660	38175388	21	0.415	C>T	0.90	0.637	A
KCNJ6	rs8129919	38176410	21	0.471	G>A	10.69	0.005	A
KCNJ6	rs2836039	38188930	21	0.195	G>A	n/a	n/a	n/a
KCNJ6	rs2836048	38206168	21	0.321	G>A	3.04	0.218	A
KCNJ6	rs2836050	38206705	21	0.227	C>T	FE	0.044	R
KCNJ6	rs3787870	38207323	21	0.463	A>G	0.07	0.966	A
KCNJ6	HapA1					0.25	0.882	
KCNJ6	HapA2					0.58	0.749	
KCNJ6	HapA3					0.22	0.895	
KCNJ6	HapB1					0.55	0.761	
KCNJ6	HapB2					3.41	0.182	
KCNJ6	HapB3					0.36	0.835	
KCNJ6	HapC1					0.51	0.777	
KCNJ6	HapC2					0.21	0.902	
KCNJ6	HapC3					0.03	0.983	
KCNJ6	HapD1					0.23	0.892	
KCNJ6	HapD4					1.27	0.529	
KCNJ6	HapD6					1.41	0.493	

Gene	SNP	Position	Chr	MAF	Alleles	Chi Square	p-value	Model
KCNJ6	HapE1					2.47	0.290	
KCNJ6	HapE2					3.42	0.181	
KCNJ6	HapE5					1.77	0.413	
KCNJ6	HapE7					1.40	0.496	
KCNJ6	HapF1					2.77	0.251	
KCNJ6	HapF2					0.01	0.993	
KCNJ6	HapF4					3.04	0.219	
KCNJ6	HapG1					1.64	0.441	
KCNJ6	HapG5					0.98	0.613	
KCNJ6	HapG6					0.08	0.962	
KCNJ6	HapH1					0.68	0.713	
KCNJ6	HapH3					1.18	0.556	
KCNJ6	HapH5					1.74	0.418	
KCNJ6	HapI1					0.14	0.932	
KCNJ6	HapI5					0.28	0.869	
KCNJ6	HapJ1					1.01	0.605	
KCNJ6	HapJ2					0.39	0.823	
KCNJ6	HapJ3					0.09	0.955	
KCNJ6	HapK1					1.18	0.554	
KCNJ6	HapK4					2.05	0.358	
KCNJ6	HapL1					1.80	0.407	
KCNJ6	HapL4					3.15	0.207	
KCNJ6	HapL5					5.77	0.056	
KCNJ6	HapM1					0.71	0.702	
KCNJ6	HapM4					1.59	0.451	
KCNJ6	HapM6					1.73	0.421	
KCNJ6	HapN2					3.44	0.179	
KCNJ6	HapN3					4.66	0.097	
KCNJ9	rs6677510	158318743	1	0.442	A>G	0.93	0.629	A
KCNJ9	rs2753268	158324876	1	0.260	C>T	3.82	0.148	A
TWO-PORE POTASSIUM CHANNELS								
KCNK2	rs2601640	213253979	1	0.492	A>G	0.92	0.630	A
KCNK2	rs12141327	213273537	1	0.335	G>A	0.44	0.802	A
KCNK2	rs1452619	213280153	1	0.120	A>G	0.64	0.725	A
KCNK2	rs10494991	213287222	1	0.331	T>C	1.57	0.456	A
KCNK2	rs1584759	213289445	1	0.453	A>C	0.75	0.687	A
KCNK2	rs12064317	213293664	1	0.136	G>T	0.26	0.880	A
KCNK2	rs6665177	213298091	1	0.155	G>A	0.14	0.933	A
KCNK2	rs12028008	213298169	1	0.497	A>G	0.34	0.842	A

Gene	SNP	Position	Chr	MAF	Alleles	Chi Square	p-value	Model
KCNK2	rs12038094	213302819	1	0.291	C>T	1.96	0.375	A
KCNK2	rs17024179	213304166	1	0.163	T>C	2.06	0.358	A
KCNK2	rs7528988	213315040	1	0.259	C>T	3.01	0.222	A
KCNK2	rs2363561	213321930	1	0.395	C>T	0.41	0.815	A
KCNK2	rs12133857	213331109	1	0.128	G>T	0.34	0.843	A
KCNK2	rs4411107	213355542	1	0.375	T>C	1.08	0.584	A
KCNK2	rs4303048	213385781	1	0.236	G>A	2.10	0.349	A
KCNK2	rs12757222	213391641	1	0.233	A>G	2.81	0.246	A
KCNK2	rs1556905	213428215	1	0.411	C>A	0.21	0.899	A
KCNK2	rs10494994	213428830	1	0.207	G>A	0.53	0.767	A
KCNK2	rs12038695	213444580	1	0.494	A>C	1.16	0.559	A
KCNK2	rs2027320	213446566	1	0.385	G>A	0.37	0.833	A
KCNK2	rs12143625	213458463	1	0.235	T>C	0.61	0.739	A
KCNK2	rs12080135	213463166	1	0.252	T>G	0.20	0.905	A
KCNK2	HapA1					0.44	0.802	
KCNK2	HapA4					0.92	0.630	
KCNK2	HapB1					1.45	0.485	
KCNK2	HapB4					0.97	0.615	
KCNK2	HapC1					0.45	0.799	
KCNK2	HapC4					1.59	0.451	
KCNK2	HapC5					0.34	0.842	
KCNK2	HapD1					0.01	0.994	
KCNK2	HapD3					0.41	0.815	
KCNK2	HapE1					0.14	0.935	
KCNK2	HapE3					1.18	0.554	
KCNK2	HapE4					0.62	0.733	
KCNK2	HapF2					0.37	0.833	
KCNK2	HapF3					1.16	0.559	
KCNK3	rs1275982	26772593	2	0.497	C>T	4.75	0.093	A
KCNK3	rs1275977	26776359	2	0.414	A>G	4.79	0.091	A
KCNK3	rs11126666	26782315	2	0.330	G>A	4.00	0.135	A
KCNK3	rs1662987	26791686	2	0.243	A>G	4.80	0.091	A
KCNK3	rs1662988	26793738	2	0.290	C>T	0.72	0.699	A
KCNK3	rs7584568	26798797	2	0.471	G>A	1.80	0.407	A
KCNK3	HapA1					4.00	0.135	
KCNK3	HapA4					4.75	0.093	
KCNK3	HapB1					1.51	0.470	
KCNK3	HapB2					4.22	0.121	
KCNK3	HapB4					0.50	0.780	

Gene	SNP	Position	Chr	MAF	Alleles	Chi Square	p-value	Model
KCNK9	rs2542424	140701683	8	0.362	A>G	4.75	0.093	A
KCNK9	rs2542422	140706306	8	0.328	C>A	0.08	0.961	A
KCNK9	rs2014712	140709816	8	0.235	C>T	1.01	0.604	A
KCNK9	rs2545462	140714686	8	0.343	C>A	0.24	0.887	A
KCNK9	rs2542420	140714883	8	0.419	C>G	0.21	0.902	A
KCNK9	rs2545461	140717431	8	0.257	A>G	n/a	n/a	n/a
KCNK9	rs3780051	140727983	8	0.471	A>G	0.12	0.943	A
KCNK9	rs2545457	140730467	8	0.350	T>C	1.43	0.489	A
KCNK9	rs2005895	140738217	8	0.256	T>C	0.34	0.842	A
KCNK9	rs888349	140738927	8	0.197	A>C	0.45	0.801	A
KCNK9	rs759656	140739149	8	0.320	T>C	n/a	n/a	n/a
KCNK9	rs13277242	140739269	8	0.495	G>A	3.84	0.147	A
KCNK9	rs885724	140740112	8	0.380	A>C	FE	0.048	D
KCNK9	rs3780039	140745846	8	0.372	T>G	FE	0.003	D
KCNK9	rs10110946	140754803	8	0.333	T>C	1.08	0.583	A
KCNK9	rs7828107	140756023	8	0.409	C>A	4.05	0.132	A
KCNK9	rs983740	140762922	8	0.472	T>G	3.72	0.156	A
KCNK9	rs11166921	140776937	8	0.395	C>A	FE	0.020	R
KCNK9	rs13278664	140779544	8	0.455	A>G	3.52	0.173	A
KCNK9	HapA1					0.16	0.925	
KCNK9	HapA2					0.13	0.938	
KCNK9	HapA3					4.28	0.118	
KCNK9	HapB1					0.09	0.957	
KCNK9	HapB4					0.13	0.939	
KCNK9	HapC1					1.13	0.568	
KCNK9	HapC3					1.54	0.464	
KCNK9	HapC4					3.85	0.146	
KCNK9	HapD1					0.42	0.812	
KCNK9	HapD2					3.18	0.204	
KCNK9	HapD3					6.60	0.037	

Abbreviations: A = additive model, Chr = chromosome, D = dominant model, Hap = haplotype, KCNA = voltage-sensitive potassium channel, KCND = voltage-gated potassium channel, KCNJ = potassium inward-rectifying channel, KCNK = potassium channel, subfamily K, MAF = minor allele frequency, n/a = not assayed because SNP violated Hardy-Weinberg expectations ($p<.001$) or because MAF was <.05, R = recessive model, SNP= single nucleotide polymorphism

Table 2

Significant Differences in Demographic and Clinical Characteristics Between Patients With (n = 110) and Without (n = 280) Preoperative Breast Pain*

Characteristic	NO PAIN Mean (SD)	PAIN Mean (SD)	Statistic and p-value
Age (years)	56.5 (11.8)	50.9 (9.8)	t=4.81; p<0.001
Karnofsky Performance Status score	94.0 (10.3)	90.9 (10.1)	t=2.66; p= 0.008
Number of biopsies in past year	1.5 (0.8)	1.6 (0.8)	U=12887.0, p<0.01
	% (N)	% (N)	
Non-white race/ethnicity	31.9 (89)	45.0 (49)	FE; p=0.018
Post-menopausal	67.9 (186)	53.8 (57)	FE; p=0.012

Abbreviations: FE = Fisher's Exact, SD = standard deviation

* Modified from McCann, B., Miaskowski, C., Koetters, T., Baggott, C., West, C., Levine, J. D., et al. (2012). Associations between pro- and anti-inflammatory cytokine genes and breast pain in women prior to breast cancer surgery. J Pain, 13, 425-437.

Table 3

Multiple Logistic Regression Analyses for Single Nucleotide Polymorphisms in KCNS1, KCNJ3, KCNJ6, and KCNK9 and the Occurrence of Preoperative Breast Pain (N=302)

Pain Group Comparison	Predictor	Odds Ratio	Standard Error	95% CI	Z	p-value
No pain (n=218) versus Pain (n=84)	KCNS1 rs4499491	3.01	1.004	1.561, 5.785	3.29	0.001
	Age	0.77	0.051	0.677, 0.878	−3.92	<0.001
	Overall model fit: $\chi^2 = 34.94$, p <.0001; $R^2 = 0.0989$					
No pain (n=218) versus Pain (n=84)	KCNJ3 rs7574878	0.52	0.165	0.276, 0.966	−2.07	0.038
	KCNJ3 Hap E1	1.69	0.408	1.049, 2.710	2.16	0.031
	Age	0.76	0.051	0.664, 0.863	−4.16	<0.001
	Overall model fit: $\chi^2 = 40.74$, p <.0001; $R^2 = 0.1154$					
No pain (n=218) versus Pain (n=84)	KCNJ6 rs2835914	0.48	0.140	0.274, 0.850	−2.52	0.012
	KCNJ6 rs8129919	2.10	0.459	1.367, 3.220	3.39	0.001
	KCNJ6 rs2836050	3.58	2.001	1.199, 10.708	2.29	0.022
	Age	0.74	0.052	0.648, 0.854	−4.20	<0.001
	Overall model fit: $\chi^2 = 46.71$, p <.0001; $R^2 = 0.1322$					
No pain (n=218) versus Pain (n=84)	KCNK9 rs3780039	1.90	0.594	1.027, 3.506	2.05	0.041
	KCNK9 rs11166921	2.40	0.830	1.218, 4.726	2.53	0.011
	Age	0.77	0.051	0.678, 0.878	−3.92	<0.001
	Overall model fit: $\chi^2 = 35.59$, p <.0001; $R^2 = 0.1008$					

Multiple logistic regression analyses of candidate gene associations with no pain versus pain. The first three principal components identified from the analysis of ancestry informative markers as well as self-reported race/ethnicity were retained in all models to adjust for potential confounding due to population substructure (data not shown). Predictors evaluated in each model included genotype (KCNS1 rs4499491: CC+CA (no pain (n=189), pain (n=58)) versus AA (no pain (n=29), pain (n=26)); KCNJ3 rs7574878: TT (no pain (n=61), pain (n=42)) versus TG+GG (no pain (n=157), pain (n=42)); KCNJ3 haplotype E1 composed of rs2591168-rs2591172: zero, one, or two doses of the A-G haplotype; KCNJ6 rs2835914: GG (no pain (n=85), pain (n=45)) versus GC+CC (no pain (n=133), pain (n=39)); KCNJ6 rs8129919: GG (no pain (n=65), pain (n=15)) versus GA (no pain (n=121), pain (n=44)) versus AA (no pain (n=32), pain (n=25)); KCNJ6 rs2836050: CC+CT (no pain (n=207), pain (n=74)) versus TT (no pain (n=11), pain (n=10)); KCNK9 rs3780039: TT (no pain (n=103), pain (n=24)) versus TG+GG (no pain (n=114), pain (n=60)); KCNK9 rs11166921: CC+CA (no pain (n=185), pain (n=61)) versus AA (no pain (n=33), pain (n=23))), and age (in 5 year increments).

Abbreviations: CI =confidence interval; Hap = haplotype; KCNJ3 = potassium inwardly-rectifying channel, subfamily J, member 3; KCNJ6 = potassium inwardly-rectifying channel, subfamily J, member 6; KCNK9 = potassium channel subfamily K, member 9; KCNS1 = potassium voltagegated channel, delayed-rectifier, subfamily S, member 1.