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COMT Val158Met Affects the Analgesic Response to Acupuncture Among Cancer Survivors with Chronic Pain

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Abstract

Catechol-O-methyltransferase (COMT) is the major enzyme involved in the catabolism of dopamine, a neurotransmitter in the brain's reward system. The common *COMT* polymorphism Val158Met (rs4680 G>A) modulates pain response to opioids through a reward-motivated mechanism; however, its role in nonpharmacological pain medicine has not been clinically characterized. We genotyped 325 participants from a randomized controlled trial of cancer survivors with chronic musculoskeletal pain. We found that carrying methionine at position 158 (158Met) of COMT, encoded by the A allele, significantly increased the analgesic response to electroacupuncture (74% versus 50%; odds ratio [OR]: 2.79; 95% confidence interval [CI]: 1.31, 6.05; p<0.01), but not to auricular acupuncture (68% versus 60%; OR: 1.43; 95% CI: 0.65, 3.12; p=0.37) or usual care (24% versus 18%; OR: 1.46; 95% CI: 0.38, 7.24; p=0.61) compared to Val/Val. These findings raise the possibility that *COMT* Val158Met might be an important predictor of analgesic response to electroacupuncture, providing novel insights into precision non-pharmacologic pain management tailored to individual genetic backgrounds.

Graphical Abstract

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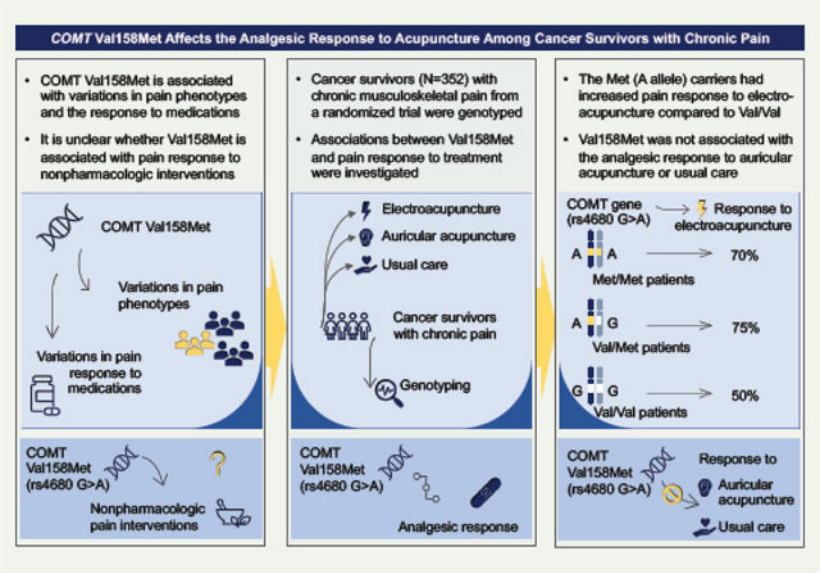

Keywords

COMT Val158Met; chronic pain; acupuncture; cancer survivors; treatment response

INTRODUCTION

Precision medicine focuses on developing prevention and treatment strategies that take into account inter-individual variability including germline gene variants,[7] and its application in oncology has contributed to the recent decrease in the global cancer mortality rate.[29, 48] The number of cancer survivors reached over 16.9 million in 2019 in the United States (U.S.), and will continue to grow; yet, over 50% of individuals affected by cancer still endure persistent and debilitating symptoms such as pain.[25, 37] Nearly one in two cancer survivors experience undertreated pain,[10, 11, 54] which can contribute to poor quality of life, impaired physical functioning, and nonadherence to cancer therapy, potentially worsening prognosis.[28, 62] While incorporating the concepts of precision medicine into survivorship symptom management has been articulated as an important aspect of cancer care, research is extremely limited.

To inform targeted treatment, pain medicine leverages information on genes and gene variants that modulate sensory, affective, and behavioral phenotypes of pain.[38, 47, 56] Catechol-O-methyltransferase (COMT) metabolizes catecholamine neurotransmitters and variants in the *COMT* gene have been linked to the regulation of pain perception, pain-related behavior such as treatment seeking and response, and adverse drug reactions.[13, 17, 49] More specifically, the single nucleotide polymorphism (SNP) *COMT* Val158Met (rs4680, G>A), plays a crucial role in regulating levels of dopamine in the brain and was reported to predict the analgesic response to opioid drugs.[8, 31, 33] rs4680 also links reward processing and anti-inflammatory/analgesic activities to nonpharmacologic pain interventions such as acupuncture in human subjects and animal models via dopamine-mediated neurobiological pathways.[26, 30, 58] Particularly, the valine (Val) at position 158 (Val158), encoded by the G

allele, has been associated with better resilience to pain and stressors, whereas individual carriers of methionine (Met) have a lower pain threshold, stronger perceptual-emotional reaction to pain (affective pain response), and a less active endogenous brain opioid response system.[24, 61]

Acupuncture is a nonpharmacologic therapy with analgesic effects well established in cancer and noncancer pain populations.[27, 55] Our recent clinical trial demonstrated that both electroacupuncture (EA) and auricular acupuncture (ARA) produced clinically meaningful and durable analgesic effects, and that EA and ARA reduced the use of oral pain medications compared to usual care (UC) for chronic musculoskeletal pain in cancer survivors.[35] Given the increasing use of acupuncture in pain care, it would be most useful to characterize the potential role of *COMT* Val158Met (rs4680 G>A) in modulating the analgesic response to treatment, as addressed in the present study. We previously found that rs4680 was associated with response to EA in 38 postmenopausal, hormone receptor-positive, breast cancer survivors with aromatase inhibitor-induced arthralgia.[22] Building on our preliminary findings, this study involves the analysis of an *a priori* SNP leveraging samples from a randomized clinical trial, and aims to determine the relationship between *COMT* Val158Met (rs4680 G>A) and the analgesic response to EA, ARA, and UC in a cohort of cancer survivors with chronic musculoskeletal pain.

METHODS

Study Design

The Personalized Electroacupuncture Versus (vs.) Auricular Acupuncture Comparative Effectiveness (PEACE) trial (ClinicalTrials.gov Identifier: NCT02979574) is a three-arm, parallel randomized clinical trial conducted from March 2017 to April 2020, across an urban academic cancer center and five suburban sites in New York and New Jersey. Patients with chronic musculoskeletal pain were randomized 2:2:1 to EA, ARA, or UC (Figure 1). Patients received ten acupuncture sessions (EA or ARA) or usual pain care over ten weeks. Germline DNA was obtained from biospecimens collected at baseline and genotyped. We evaluated associations between a functional genetic polymorphism and patient-reported response to pain treatment at 12 weeks. Details have been previously reported,[34, 35] and in relation to the current study, are summarized below. The Institutional Review Board at Memorial Sloan Kettering Cancer Center approved all study procedures. Participants provided informed consent, including collecting biospecimens for genetic analyses before enrollment into the trial.

Participants

Inclusion Criteria: We included adult patients who: 1) were English-speaking, 2) had a prior cancer diagnosis and no current evidence of disease, 3) experienced musculoskeletal pain for at least three months and at least 15 days in the preceding 30 days, and 4) rated their worst pain intensity in the past week as moderate or greater (≥4 on a 0–10 numerical rating scale).

Exclusion Criteria: We excluded patients with: 1) inflammatory arthritis requiring disease-modifying drugs; 2) phantom limb pain; 3) a pending pain-related Veteran Health Administration, social security, or worker's compensation disability claim by self-report; or 4) an implanted electronically charged medical device.

Interventions

EA: Licensed acupuncturists with more than five years of experience in oncology settings delivered ten weekly sessions of semi-standardized, protocolized treatment. Acupuncture needles (SEIRIN) were inserted at the selected points after skin disinfection, and then manually manipulated to achieve De Qi sensation (a feeling of tingling and numbness at the needle site). An A3922 E-STIM II device (Tens Plus Industrial Company) delivered electrical stimulation at 2Hz to four points near the pain location. All needles were withdrawn after a 30-minute retention.

ARA: The same acupuncturist team also delivered the protocolized ARA developed by the U.S. military, known as battlefield acupuncture.[39] Prior to needle placement, the auricular skin was sterilized and up to ten needles were administered for ten fixed auricular points based on an individual patient's pain reactions to treatment. The total duration of each treatment session was approximately 10 to 20 minutes, depending on how many needles were administered. The needles remained in place for three to four days. Patients were instructed on how to remove the needles safely. Patients received ten treatments over ten weeks. Patients in the EA or ARA groups were not required to stop receiving usual pain care but were instructed to record the other pain treatments they received throughout the study period.

UC: Patients received standard care for their pain as prescribed by their healthcare clinicians, including analgesic medications, physical therapy, and glucocorticoid injections. Patients were offered the option of receiving ten acupuncture treatments after week 12 (duration of the primary end point).

Outcome Measures

The primary outcome was the change in the Brief Pain Inventory (BPI) pain severity score from baseline to week 12. The BPI is an 11-item pain assessment tool validated for use with cancer patients.[5] It measures the severity of pain (four items) and interference (seven items) of pain. The BPI psychometrics are well-established (Cronbach's alpha 0.80–0.87 for the four pain severity items and 0.89–0.92 for the seven interference items [6]). A reduction of 30% or greater on the BPI pain severity score after treatment was considered an analgesic response.[16, 57]

Biospecimen Procurement and Genotyping

Blood samples were drawn at baseline in EDTA tubes. Individuals who could not have blood drawn or refused a blood draw provided saliva using Oragene•DISCOVER (OGR-500) collection kits (DNA Genotek Inc.) following the manufacturer's recommendations and study coordinator's guidance. Samples were received by the Molecular Epidemiology/Orlow Lab at MSK where DNA was extracted with the Qiagen QIAamp DNA Blood Kit (blood),

and the PrepIT-L2P purifier (saliva), following manufacturers' directions and existing laboratory standard operating procedures. DNA quantity and quality were measured with the Nanodrop ND8000 (total DNA), and with the Qubit® DNA Assay kit and Qubit® 2.0 Fluorometer (Life Technologies) for double stranded DNA (dsDNA). Fragmentation and amplifiability were estimated with a QC-PCR and with smear analysis.[53]

COMT rs4680 G>A (Val158Met) was genotyped using the MassArray iPLEX chemistry and platform (Agena Bioscience). Custom oligos were purchased from Integrated DNA Technologies (IDT). Common PCR reagents and previously published methods and QA/QC procedures were utilized.[9, 40] Genotyping included internal laboratory controls and was performed blinded to the clinical trial arms/status. Data were reported according to the presence of two (GG, Val/Val), one (GA, Val/Met), or no reference alleles (AA, Met/Met). The genotyping success rate was 99.4%, and the prevalence of the minor allele in this cohort, regardless of outcome, was 43% (minor allele frequency, or MAF=0.430). Hardy-Weinberg equilibrium (HWE) was evaluated with chi-squared tests, and no departure from HWE was noticed (p=0.07); however, only a several order magnitude departure would have been of interest as our study did not include unaffected (no cancer history) individuals or a control population.

Statistical Analysis

We reported the clinical characteristics of patients using descriptive statistics (means, standard deviations, frequencies, and proportions). We used chi-squared tests to evaluate HWE (a $p<0.05$ is considered inconsistent with the HWE). We assessed the crude association between SNP rs4680 and analgesic response within the treatment arm by comparing the proportion of responders among patients carrying different genotypes using cross-tabulations and chi-square tests. Fisher's exact tests were used when cells had fewer than five patients.

We used separate logistic regression models for each treatment arm (EA, ARA, and UC) to estimate the within-arm associations between rs4680 and analgesic response. We estimated unadjusted associations as well as associations adjusting for sex and race (White vs. non-White). Results for these models are presented as ORs with 95% CIs. The effect of the minor (A) rs4680 allele on the response to treatment was assessed considering the additive (GG vs. GA vs. AA), dominant (GG vs. GA/AA), and recessive models (GG/GA vs. AA). Briefly, in the additive model, the assumption is that the effect increases k-fold for GA compared to GG, and by 2k-fold for AA. In the dominant model, we considered A as the dominant allele and genotypes GG vs. GA/AA were analyzed as a dichotomous variable, assuming that the two genotypes carrying one or two A alleles had the similar response rate.[1, 12] The recessive model assumed that two AA alleles are required to exert a response compared to GA/GG. To test whether the association between rs4680 genotypes and analgesic response differed by treatment arm (EA vs. ARA), we fit similar additive, dominant, and recessive models that included rs4680, treatment arm (EA vs. ARA), and the rs4680*arm interaction. The UC arm was omitted from these interaction models because UC patients did not have statistically significant improvement in pain outcomes in the analysis of the PEACE trial primary endpoint.[35]

We used multivariable logistic regression to assess the association between rs4680 and analgesic response to EA or ARA or UC, adjusting for sex and race (White vs. non-White). Results for these models are presented as ORs with 95% CIs. P-values less than 0.05 were considered statistically significant. The sample size of the parent trial was selected to yield at least 90% power for detecting at least 30% difference in response rates between the Met (or A allele) carriers and non-carriers while maintaining an overall Type I error rate of 5% for the comparisons. Data analysis was performed using R version 4.1.2.[52]

RESULTS

Demographics and Genotypic Information at Baseline

Leveraging data from our recently completed PEACE randomized clinical trial,[35] of the 360 randomized patients, 325 provided blood or saliva biospecimens for extraction of germline DNA and genetic testing, and 323 were successfully genotyped for rs4680 (Figure 1). After further exclusion of participants due to missing pain response status, data were available for 317 patients (Figure 1). Patients were well balanced across treatment arms regarding demographics and baseline characteristics except for race (Table 1). The overall minor allele frequency (MAF) in our cohort (0.45) was similar to the MAF reported in the general non-Hispanic White population (0.47), and there were no differences in the prevalence of the A (AA or GA) allele across the three intervention arms (p=0.6) (Table 2).

Association Between *COMT* Val158Met (rs4680 G>A) and Analgesic Response

In the EA group, under the dominant model, patients carrying one or two *COMT* rs4680 minor alleles (AA or GA) had a significantly higher analgesic response rate compared to those who were homozygous GG (73.6% vs. 50%, p=0.007) (Table 3, Figure 2). Multivariable logistic regression analysis showed that the association remained significant after adjusting for sex and racial status (adjusted OR: 2.57; 95% CI: 1.17, 5.71; p=0.019) (Table 4). The differences in response to treatment were also significant under the additive model (unadjusted OR per-allele: 1.76; 95% CI: 1.02, 3.10; p=0.045), but not the recessive model (unadjusted OR_{AA}: 1.21; 95% CI: 0.47, 3.37; p=0.71) (Supplementary Tables S1 & S2; see Supplementary Figure S1 & S2 **for individual pain data**). After controlling for sex and race, the additive model association between the genotypes and response to treatment no longer met the threshold for statistical significance (adjusted OR per-allele: 1.64; 95% CI: 0.94, 2.93; p=0.087).

In the ARA or UC groups, the A allele did not lead to a significantly higher response rate than the homozygous G allele under either the dominant model (ARA: unadjusted OR: 1.43; 95% CI: 0.65, 3.12; p=0.37; UC: unadjusted OR: 1.46; 95% CI: 0.38, 7.24; p=0.61) (Table 4) nor the additive model (ARA: unadjusted OR per-allele: 1.46; 95% CI: 0.80, 2.71; p=0.22; UC: unadjusted OR per-allele: 1.32; 95% CI: 0.53, 3.36; p=0.54) (Supplementary Tables S1). The response to ARA or UC treatment was not associated with the *COMT* genotype under the recessive model (ARA: unadjusted OR_{AA}: 2.07; 95% CI: 0.60, 9.53; p=0.29; UC: unadjusted OR_{AA}: 1.43; 95% CI: 0.27, 6.03; p=0.64) (Supplementary Tables S2). The interaction between the treatment arm (EA vs. ARA) and rs4680 genotype for

predicting analgesic response was not statistically significant in the dominant (p=0.23), additive model (p=0.65), or recessive model (p=0.52).

DISCUSSION

Using biomarkers and patient-reported outcomes from a randomized clinical trial of EA, ARA, or UC among cancer survivors with chronic musculoskeletal pain, we demonstrated a genotype-dependent analgesic treatment response to EA. In particular, carrying one or two Met alleles in position 158 of *COMT* (rs4680 A/AA) improved the response to EA, but not to ARA or UC. This indicates that such a response cannot be explained by regression to the mean and may be specific to the EA as an intervention. Our findings are plausible because COMT is central in modulating synaptic dopamine levels, affecting pain perception and natural analgesia, and because rs4680 is also linked to pain response to opioid analgesics. Given the growing number of cancer survivors; the significant proportion of individuals with debilitating pain who remain undertreated; and the very high costs, side effects, and risks of opioid-based pain care, these findings have important implications. As germline genetic testing is increasingly common in oncology clinical care,[45] our findings may be used to develop future precision cancer pain management approaches.

Our findings provide evidence of *COMT* Val158Met as a potential genetic predictor of analgesic response to electroacupuncture. The presence of methionine at position 158 of COMT reduces the rate at which pain-modulating neurotransmitters like dopamine, epinephrine, and norepinephrine are degraded.[15, 42] As such, rs4680 has not only been considered a genetic indicator of pain phenotypes but is also linked to pain response to pharmacological interventions.[43, 50] Our findings are consistent with previous pharmacogenetic evidence: the A (Met) allele alone or as a part of a haplotype is associated with reduced opioid use for cancer pain and postoperative pain.[4, 32, 36, 44] Important evidence from a prospective randomized clinical trial highlighted that temporomandibular joint pain patients with low activity *COMT* haplotypes (containing rs4680 A allele) experienced greater pain reductions by propranolol vs placebo than patients with other *COMT* haplotype.[51] Acupuncture also produces a more adequate response in carriers of the A (Met) allele with insomnia disorder relative to the response observed in those carrying the G (Val) allele.[21] Similar to the drug and food reward, the effect of EA may be encoded as a reward to treatment-seeking behaviors in the central nervous system by the descending pain modulatory system (DPMS).[18, 19] However, we did not observe such a response to ARA; this raises the interesting possibility that different modes of mechano-sensory stimulation may have varying underlying mechanisms.

According to the motivation-decision model,[18, 19] the Met allele reduces the release of reactive phasic dopamine and leads to low availability of endogenous opioids, causing higher pain and greater psychological distress.[2, 46, 61] Primary mechanistic research using animal or human models found that EA directly regulates the endogenous opioid release and the expression of dopamine D2-like receptors in the peripheral, spinal, and supraspinal levels to reduce acute and chronic pain.[60] Therefore, the allelic effect observed may be explained by the effect of electroacupuncture on the release of endogenous opioids. Acupuncture may also ameliorate neuroinflammation and astrogliosis linked to heightened

catecholaminergic tone in a persistent pain model induced by the inhibition of COMT, which experimentally mimics the low-activity *COMT* Met allele.[30] Additionally, studies of brain imaging showed that the low-activity 158Val might be associated with the effect of EA on the functional connectivity of the brain default mode network with the left middle frontal gyrus,[58] which processes human reward response in adulthood.[57] Based on our observations and data,[22] plus the aforementioned reports regarding pain and dopaminergic signaling, the current findings suggest that a reward-motivated neurobiological mechanism partially modulates the impact of rs4680 on the analgesic response to EA. Our study findings extend the clinical applicability of these mechanistic insights of EA and suggest that certain individuals with *COMT* Val158Met (rs4680 G>A) genetic signature are likely to benefit from EA for pain management.

Strengths and Limitations

This prospective investigation was designed to validate a hypothesis based on our preliminary findings.[22] Additional strengths of our work include the study design. Specifically, we used data from a rigorously conducted randomized controlled trial where treatment fidelity was monitored, and missing data was low. Also, the sample of cancer survivors was further balanced in terms of gender, tumor types, and treatment history, with good minority representation. We used protocolized interventions that reflect real-world practice, which resulted in high patient compliance (EA 93.8%; ARA 81.8%) and a low dropout rate (5.6%).[35] Further, our sample size was larger compared to previous interventional studies.[3, 41]

This research, however, is subject to some methodological limitations. First, this study was designed as a comparative effectiveness trial, so we did not have sham control. We have usual care control for any potential Hawthorne effect or regression to the mean effect as well as another intervention (i.e. auricular acupuncture). Providers and patients were not blinded to the treatment arms, combined with the mixed treatment options patients in the usual care group received, our study design did not allow us to tease out the specific needling effect from the non-specific therapeutic effect. Second, while we used validated patient-reported outcomes, we did not have objective pain measurements to phenotype specific pain sensations and neurobiological processes. Quantitative sensory testing and conditioned pain modulation assessment could be included in future studies.[14, 20] A third limitation is the lack of multiple comparison corrections, given that three genetic models were tested for each group. Further, we did not infer ancestry by multi-locus genotyping. Despite our analyses adjusted for White and non-White racial categories, residual confounding may present for ancestry heterogeneity. While not a methodological limitation, by design, we aimed to validate the preliminary findings of our pilot study, focusing on the role of the common *COMT* Val158Met (rs4680 G>A) in leading the analgesic response to acupuncture. Recognizing pain genetics is complex, future studies need to identify and validate other genetic variants associated with acupuncture analgesic response.

CONCLUSION

Among cancer survivors with chronic musculoskeletal pain, *COMT* Val158Met encoded by rs4680 is associated with the analgesic response to electroacupuncture. It raises the possibility that *COMT* Val158Met is an important predictive biomarker of analgesic response. These findings also offer potential neurobiological insights into the reward-motivated changes in pain behavior during nonpharmacologic treatment. Future research using translational strategies can help further develop the field of precision pain management for cancer survivors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest:

JJM reports grant from Tibet Cheezheng Tibetan Medicine Co. Ltd. outside the submitted work. KSP reports stock ownership in Johnson & Johnson, Pfizer, Viking Therapeutics, and Catalyst Biotech outside the submitted work. The other authors have no disclosures.

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Highlights

- Prespecified genotype analysis of *COMT* Val158Met among 325 cancer survivors with chronic pain
- Val/Met and Met/Met increased the analgesic response to electroacupuncture compared to Val/Val
- Val158Met was not associated with the analgesic response to auricular acupuncture or usual care

Perspective:

This work suggests the modulating effects of the polymorphism in *COMT* Val158Met on the response to acupuncture. Further research needs to validate these findings, increase the mechanistic understanding of acupuncture, and guide further development of acupuncture as a precision pain management strategy.

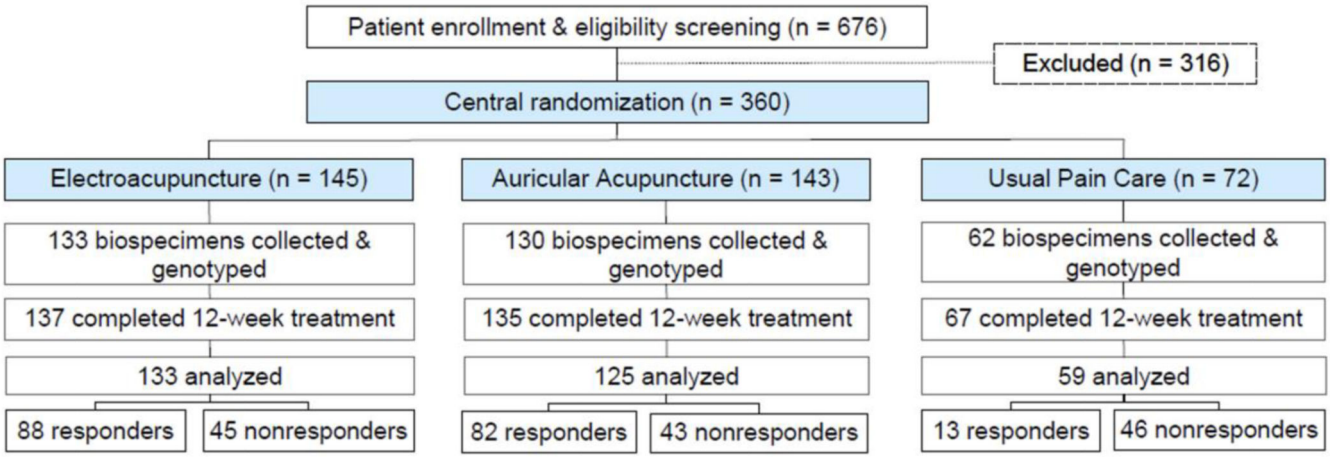

Figure 1. Study flow chart

Flow chart summarizes the study design showing treatment arms, attrition, and study phases including enrollment, intervention allocation, follow-up, and data analysis.

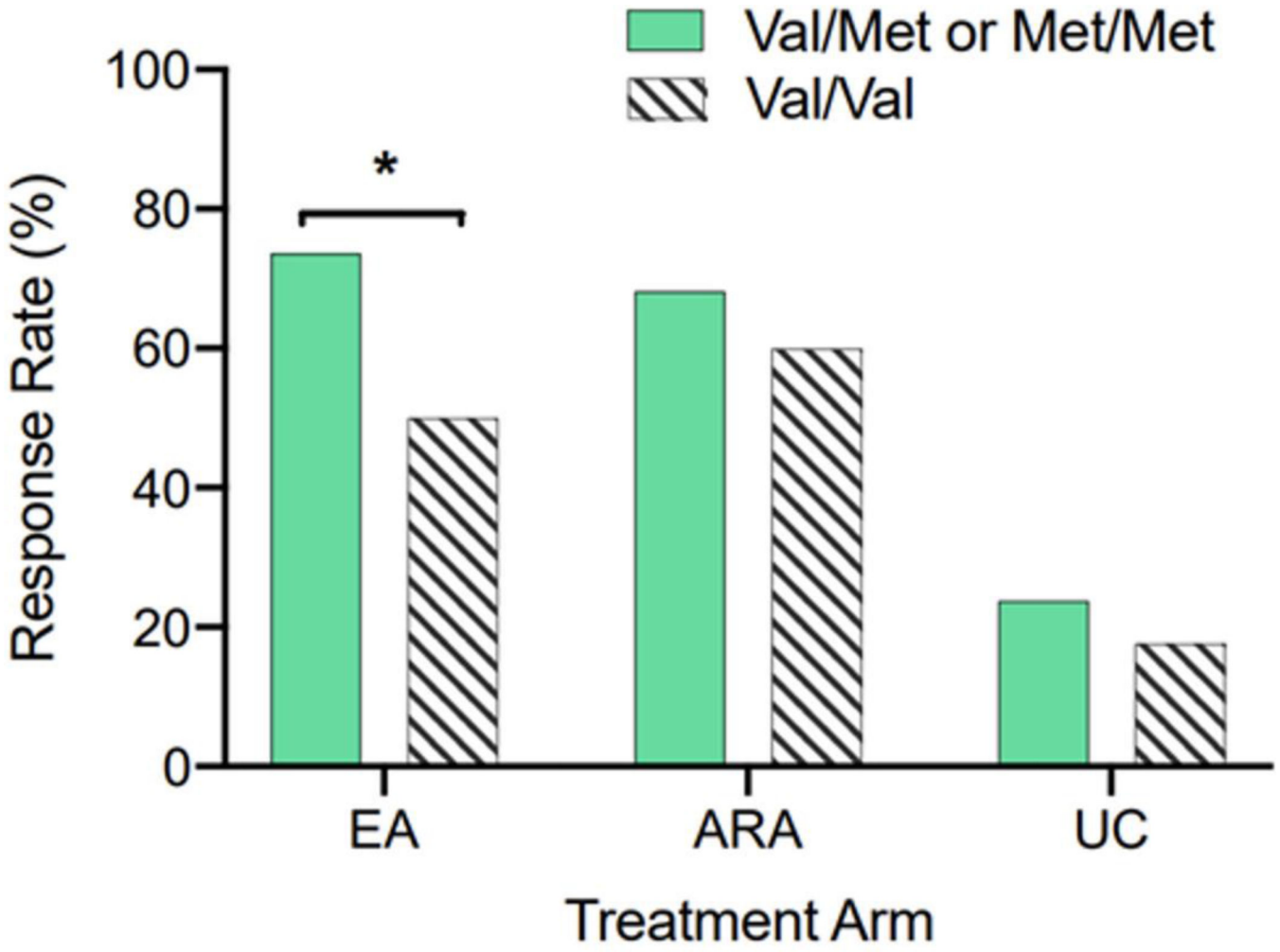

Figure 2: Analgesic response to pain care among cancer survivors enrolled in the PEACE randomized clinical trial, according to COMT Val158Met (rs4680 G>A) variants and treatment arm

Pain response rate by genotype and the types of treatment. Of the 360 patients who were randomized in the parent trial, 325 provided blood or saliva biospecimens for extraction of germline DNA/genetics, and 323 were successfully genotyped for rs4680. The multivariate logistic regression model was used during statistical analysis and P-values less than 0.05 were considered statistically significant.

Key: * p-value <0.05. P-values are calculated based on the Pearson's chi-squared tests.

Abbreviations: EA, electroacupuncture; ARA, auricular acupuncture; UC, usual care.

Table 1.

Demographic and clinical characteristics of PEACE participants by treatment arm

	Electroacupuncture Total, n=133	Auricular Acupuncture Total, n=125	Usual Care Total, n=59
Sex			
Male	39 (29.3)	39 (31.2)	15 (25.4)
Female	94 (70.7)	86 (68.8)	44 (74.6)
Race Non-White	40 (32.5)	29 (23.2)	8 (13.6)
White	93 (67.5)	96 (76.8)	51 (86.4)
Cancer type Non-Breast Cancer	73 (54.9)	63 (50.4)	32 (54.2)
Breast Cancer	60 (45.1)	62 (49.6)	27 (45.8)
Baseline BPI Pain Severity[1]	5 (3.8, 6.2)	5 (3.8, 6.0)	5 (4.5, 6.4)
Pain type Localized	80 (60.2)	70 (56.0)	37 (62.7)
Generalized[2]	53 (39.8)	55 (44.0)	22 (37.3)
Pain site Limbs	55 (41.4)	50 (40.0)	(49.2)
Trunk	78 (58.6)	75 (60.0)	(50.8)
Response at 12 weeks Responder	88 (66.2)	82 (65.6)	13 (22.0)
Non-Responder	45 (33.8)	43 (34.4)	46 (78.0)

Data are presented as n (%) or

[1]median (inter-quartile range/IQR). For each variable, column percentages sum to 100%. BPI, Brief Pain Inventory pain severity subscale.

[2]Localized pain is defined as the number of pain locations less than 5, whereas generalized pain is categorized as the number of pain sites greater than or equal to 5.[22]

Table 2.

Demographic and clinical characteristics of PEACE participants by *COMT* Val158Met (rs4680 G>A) variants

	GG (Val/Val) Total, n=99	GA (Val/Met) Total, n=170	AA (Met/Met) Total, n=48	p-value[2]
Sex				0.10
Male	33 (35.5)	52 (55.9)	8 (8.6)	
Female	66 (29.5)	118 (52.7)	40 (17.9)	
Race				**0.003**
Non-White	36 (46.8)	32 (41.6)	9 (11.7)	
White	63 (26.2)	138 (57.5)	39 (16.2)	
Cancer Type				0.4
Non-Breast Cancer	48 (28.6)	96 (57.1)	24 (14.3)	
Breast Cancer	51 (34.2)	74 (49.7)	24 (16.1)	
Treatment				0.6
Usual Care	17 (28.8)	31 (52.5)	11 (18.6)	
Auricular Acupuncture	40 (32.0)	71 (56.8)	14 (11.2)	
Electroacupuncture	42 (31.6)	68 (51.1)	23 (17.3)	
Pain Location				>0.9
Limbs	41 (30.6)	72 (53.7)	21 (15.7)	
Trunk	58 (31.7)	98 (53.6)	27 (14.8)	
Pain Type[1]				0.6
Localized	61 (32.6)	96 (51.3)	30 (16.0)	
Generalized	38 (29.2)	74 (56.9)	18 (13.8)	
Baseline Pain Severity, med (IQR)	5 (4.0, 6.4)	5 (4.0, 6.2)	5 (4.0, 5.9)	0.6

Data are presented as n (%) except for baseline pain severity, expressed as median (inter-quartile range) based on the Brief Pain Inventory pain severity subscale. Row percentages sum up to 100%.

[1]Localized pain is defined as the number of pain locations fewer than 5, whereas generalized pain is categorized as the number of pain sites greater than or equal to 5.[22]

[2]P-values correspond to Pearson's chi-squared tests for categorical variables and Kruskal-Wallis rank sum tests for continuous variables.

Table 3.

Response to pain care in PEACE participants by *COMT* Val158Met (rs4680 G>A) status within each treatment arm

	Electroacupuncture			Auricular Acupuncture			Usual Care		
	n[1]	Responder	p-value	n[1]	Responder	p-value	n[1]	Responder	p-value
			0.025 [2]			0.48[3]			0.91[3]
GG, 0 Met AG, het Val/Met AA, Met/Met	42	21 (50)		40	24 (60)		17	3 (18)	
	68	51 (75)		71	47 (66)		31	7 (23)	
	23	16 (70)		14	11 (79)		11	3 (27)	
			0.007 [2]			0.37[2]			0.74[3]
GG, 0 Met AA/AG, 1–2 Met	42	21 (50)		40	24 (60)		17	3 (18)	
	91	67 (74)		85	58 (68)		42	10 (24)	
			0.70[2]			0.38[3]			0.69[3]
GG/AG, 0–1 Met AA, Met/Met	110	72 (65.5)		111	71 (64)		48	10 (20.8)	
	23	16 (69.6)		14	11 (78.6)		11	3 (27.3)	

Het, heterozygote; Val, valine; Met, methionine. Data are presented as n (%) of patients with the given treatment arm + genotype combination who demonstrated a pain response to treatment. Homozygotes were combined with heterozygotes according to the presence of one or two A (Met) in the dominant model, and none or one A (Met) in the recessive model.

[1]Number of patients with the genotype within the treatment arm. P-values were obtained from

[2]Pearson's Chi-squared or

[3]Fisher's exact tests of differences within treatment arm in pain response proportions across genotypes.

Table 4.

Association of *COMT* Val158Met (rs4680 G>A) variants with Brief Pain Inventory response among PEACE participants, by treatment arm, using a dominant model

	Electroacupuncture			Auricular Acupuncture			Usual Care		
	n	**OR (95% CI)**	**p-value**	**n**	**OR (95% CI)**	**p-value**	**n**	**OR (95% CI)**	**p-value**
Unadjusted model[1]	42	1 (Ref)	—	40	1 (Ref)	—	17	1 (Ref)	—
GG, 0 Met AA/AG, 1–2 Met	91	**2.79 (1.31, 6.05)**	**0.008**	85	1.43 (0.65, 3.12)	0.37	42	1.46 9(0.38, 7.24)	0.61
Adjusted model[2] GG, 0	42	1 (Ref)	—	40	1 (Ref)	—	17	1 (Ref)	—
Met AA/AG, 1–2 Met	91	**2.57 (1.17, 5.71)**	**0.019**	85	1.30 (0.57, 2.91)	0.52	42	1.45 (0.32, 8.03)	0.64

Met, methionine; n, number. Homozygotes were combined with heterozygotes in the dominant model according to the presence of one or two A (Met) alleles. Unadjusted/adjusted OR, 95% CI, and p-values are shown for patients carrying one or two A (Met) alleles relative to patients carrying none.

[1] Unadjustedlogistic regression models.

[2] Adjusted logistic regression models controlled for sex and race.