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μ-Opioid Receptor Gene A118G Variants and Persistent Pain Symptoms among Men and Women Experiencing Motor Vehicle Collision

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Abstract

The mu-opioid receptor 1 (OPRM1) binds endogenous opioids. Increasing evidence suggests that endogenous OPRM1 agonists released at the time of trauma may contribute to the development of post-traumatic musculoskeletal pain (MSP). In this prospective observational study we evaluated the hypothesis that individuals with an AG or GG genotype at the *OPRM1* A118G allele, which results in a reduced response to opioids, would have less severe MSP six weeks after motor vehicle collision (MVC). Based on previous evidence, we hypothesized that this effect would be sex-dependent and most pronounced among women with substantial peritraumatic distress. European American men and women ≥18 years of age presenting to the emergency department after MVC and discharged to home after evaluation (n=948) were enrolled. Assessments included

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genotyping and six week evaluation of overall MSP severity (0–10 NRS). In linear regression modeling a significant A118G allele × sex interaction was observed: an AG/GG genotype predicted reduced MSP severity among women with substantial peritraumatic distress (β= −0.925, p=0.014), but not among all women. In contrast, men with an AG/GG genotype experienced increased MSP severity at six weeks (β=0.827, p=0.019). Further studies are needed to understand biologic mechanisms mediating observed sex differences in A118G effects.

Keywords

Opioid induced hyperalgesia; A118G; OPRM1; Motor vehicle collision; Pain

Introduction

More than 11 million Americans experience motor vehicle collision (MVC) each year; four million of these individuals present to US emergency departments after the MVC for evaluation.[11] More than 90% of these individuals are discharged to home without fracture or other identifiable injury,[39] yet persistent musculoskeletal pain (MSP) in this population is a common and costly public health problem.[13] Mechanisms of chronic MSP development remain poorly understood.

One mechanism which may contribute to the development of chronic MSP after MVC is neuronal sensitization by endogenous opioids. Stressful events such as MVC have been shown to trigger the release of endogenous opioids.[26, 49] The binding of endogenous opioids to μ-opioid receptors such as the mu-opioid receptor 1 (OPRM1) has been shown to produce a bimodal response: initial analgesia followed by more persistent opioid-induced hyperalgesia[3, 14, 25, 26] (i.e., persistent OIH). The most common genetic variant in the OPRM1 receptor is A118G;[33] the presence of a G nucleotide at A118G has been shown to result in reduced OPRM1 receptor binding affinity[6, 42] and less OPRM1 receptor expression.[24] This results in less mRNA in response to OPRM1 binding in those with a G allele, and a relative decrease in opioid effect.[22, 29] Thus those with one or more copies of the G allele at A118G would be expected to be protected from the downstream cellular effects of endogenous opioids that result in persistent hyperalgesia after stress exposure. Consistent with this hypothesis, a recent study found that women sexual assault survivors with one or more copies of the G allele at A118G were found to have a reduced MSP burden six weeks after sexual assault compared to those with an AA genotype.[4]

Currently, human data supporting the contribution of endogenous OIH to persistent pain after stress exposure is limited to the single study of sexual assault survivors referenced above. The findings have not been replicated, and, in addition, no studies have assessed for evidence that the contribution of OIH to persistent pain outcomes is a more general phenomena that may apply to other stress exposures aside from rape. In the present analysis we used the A118G genetic variant to evaluate our primary hypothesis that OIH contributes to persistent MSP after MVC. Because of substantial evidence that the effect of OIH is sex-dependent (including those of A118G[17, 36]), and because the G allele was found to be protective against persistent MSP among women sexual assault survivors, we hypothesized

that the protective effect of one or more copies of the G allele would be greater in women. In addition, because stress severity has been found to influence the magnitude of endogenous opioid release,[26, 37, 41, 46] we hypothesized that OIH (and therefore the protective effect of a G allele at A118G) would be greater among women with substantial peritraumatic distress in the early aftermath of MVC. (All women sexual assault survivors in the previous study experienced substantial distress.[4]) Finally, because of evidence that clinical pain states may result in OIH,[2, 15, 43] in secondary analyses we evaluated for evidence of a greater protective effect of A118G among individuals who reported high levels of pain prior to the MVC.

Methods

Study design and population

The details of the MVC study have been reported. In brief, individuals > 18 and ≤ 65 years of age presenting to one of eight emergency departments in four no-fault insurance states within 24 hours of MVC who did not have fracture or other injury requiring hospital admission were enrolled. Patients who were not alert and oriented were excluded, as were pregnant patients, prisoners, patients unable to read and understand English, patients taking a β-adrenoreceptor antagonist, or patients taking opioids above a total daily dose of 30 mg of oral morphine or equivalent. In addition, because genetic analyses are potentially biased by population stratification,[12] enrollment was also limited to non-Hispanic whites (the most common ethnicity at study sites). Informed consent was obtained from all participants and IRB approval was obtained at all study sites.

DNA collection and genotyping

Study personnel collected blood samples at the time of enrollment using PAXgene DNA tubes. Following DNA purification (PAXgene blood DNA kit, QIAGEN, Valencia, CA, USA), genotyping using the Sequenom platform (Sequenom, San Diego, CA, USA) was performed at rs 1799971 (A118G). Two Hapmap samples and 2 repeat samples were included in each genotyping batch (of 96 samples). Repeated genotyping demonstrated >98% call agreement.

Assessments

Overall pain intensity in the emergency department and during the month prior to MVC were assessed using verbal 0–10 numeric rating scales (NRSs). Verbal scores have advantages in acute care settings, and verbally administered NRSs have been validated as a substitute for Visual Analog Scales in the emergency department.[7] Past pain scores were calculated by summing the 0–10 pain severity scores from each of 20 body regions (scale of 0–200). Individuals reporting a score of 10 or more were defined as having high levels of past pain. This cut-off of 10 was used because (1) this represents the top quartile of pre-MVC pain in this relatively young, healthy study cohort, (2) although the scale has a high upper range, a score of 10 represents several regions of moderate or severe pain or a large number of body regions with some pain. (Average overall pain intensity in the past week (0–10 NRS) was evaluated six weeks after the MVC via web-based questionnaire or telephone interview. Stress severity in the emergency department was measured using the Peritraumatic Distress Inventory.[9] The Peritraumatic Distress Inventory is a 13 item

questionnaire assessing life threat, loss of control, helplessness/anger, and guilt/shame that results in a score between 0–52. Individuals with a score of 23 or higher were considered to have significant peritraumatic distress.[35]

Statistical Analysis

Sample sociodemographic characteristics were summarized using standard descriptive statistics. Linear regression models were used to compare pain intensity levels six weeks following MVC in individuals with AA vs GA/GG genotypes at *OPRM1* polymorphism rs1799971. To adjust for potential confounding factors, models were adjusted for age, income, education, and emergency department study site by adding them as independent variables to the model. Emergency department study site was added as a categorical variable and thus resulted in eight distinct variables in the models. Because they are not of interest or relevant to the study hypotheses other than as potential confounders, categorical variables representing study site location are not shown in the tables. Additionally, to adjust for any effect of A118G on pain prior to MVC or on acute pain, models were also adjusted for pain at the time of initial evaluation and pain prior to MVC.

In addition to primary analyses, subgroup analyses were performed on subsets of individuals with a) peritraumatic distress and b) high prior pain. Statistical significance of A118G effect was determined via linear regression model t-statistic. Covariate-adjusted least-square means and corresponding standard errors for pain scores according to A118G genotype were also obtained from model outputs. All statistical analyses were completed using SPSS software (v.21; SPSS Inc, Chicago, IL). P-values < 0.05 were considered statistically significant.

Results

Study Enrollment, Follow-Up, and Genotyping

A total of 10,629 patients were screened, 1,416 were eligible, 969 consented to study participation and 948 completed baseline evaluation. Six week follow-up assessments were completed on 859/948 (91%) of enrolled patients. All study participants provided blood for DNA genotyping; the genotyping call rate at A118G was >98% and the SNP was in Hardy-Weinberg equilibrium. Consistent with HapMap database and a previous large population-based study,[8] the prevalence of the G allele at A118G this European American sample was ~23% (214/948).

Characteristics of the Study Sample

Characteristics of the study sample are shown in Table 1. Most individuals had completed at least some college, were married, worked full time, and had an annual income of $40,000 or more. Fractures were present in 1/948 (<1%, phalanx fracture) participants, a small laceration was present in 53/948 (6%) participants. The vast majority of study participants had musculoskeletal strain only. More than one third of participants (355, 37%) reported substantial peritraumatic distress in the emergency department, nearly three quarters of those with peritraumatic distress (256, 72%) were female. There was no difference in

peritraumatic distress symptom severity among individuals without and with one or more G alleles (19.1 (9.9) vs. 19.2 (10.3), t = 0.140, p =0.886).

Evaluation for sex-dependent influence of A118G on 6 week MSP outcomes

We first evaluated whether the influence of A118G on six week MSP outcomes was sex-dependent. As shown in Table 2, a significant allele-sex interaction was observed (β = 1.059, p = 0.017). All remaining analyses were therefore stratified on patient sex.

Influence of A118G Genotype on 6 week MSP outcomes among all women and among women with substantial peritraumatic distress

The influence of A118G on six week MSP outcomes among women study participants (n = 575) is shown in Table 3. Point estimates for overall MSP six weeks after MVC were lower among women with one or more copies of the G allele at A118G (4.0 (3.5, 4.6) vs 4.3 (3.4, 4.7), p = 0.304), but no statistically significant difference was observed. When analyses were limited to women with substantial peritraumatic distress (n = 256), the protective effect of having one or more G alleles was more pronounced and statistically significant. Women with peritraumatic distress and one or more copies of the G allele had lower overall MSP six weeks after MVC than those with an AA genotype (3.6 (2.9, 4.8) vs 4.7 (4.1, 5.3), p = 0.014, Figure 1).

Influence of A118G Genotype on 6 week MSP outcomes among all men and among men with substantial peritraumatic distress

The influence of A118G on six week MSP outcomes among male study participants (n = 373) is shown in Table 3. In contrast to women, men with one or more copies of the G allele at A118G had increased overall MSP six weeks after MVC (4.0 (3.3, 4.7) vs. 3.1 (2.7, 3.5), p = 0.019). When analyses were limited to men with substantial peritraumatic distress (n = 99, Table 3), point estimates for overall MSP six weeks after MVC were higher among those with one or more copies of the G allele than those with an AA genotype (4.5 (2.2, 6.7) vs. 4.1 (2.6, 5.6), p = 0.672, Figure 1), but no statistically significant difference was observed.

Secondary analyses evaluating A118G genotype influence on 6 week MSP outcomes among individuals with a history of pre-MVC pain

Secondary analyses evaluated for the presence of OIH among individuals who reported the greatest pain severity prior to MVC (average MSP severity during the month prior to MVC in this top quartile was 22.5 (14.7)). Among women with the highest pain severity prior to MVC (n = 97, Table 4a), mean overall MSP score six weeks after MVC was lower among those with one or more copies of the G allele at A118G (2.4 (0.7, 4.1) vs 4.1 (2.9, 5.2); p = 0.028). Point estimates for mean MSP score six weeks after MVC were higher for men with substantial pain prior to MVC (n = 50, Table 4a) and at least one G allele at A118G, however this difference was not statistically significant (6.5 (4.4, 8.7) vs 5.4 (4.4, 6.4); p = 0.310, data not shown).

Discussion

To our knowledge, this is the first study evaluating the effect of a genetic variant influencing opioid system function on persistent MSP symptoms after MVC. In a previous study of European American women sexual assault survivors, all of whom had substantial peritraumatic distress,[4] those with a common genetic polymorphism in *OPRM1* which reduces the biological effect of receptor binding (one or more G alleles at A118G) experienced less MSP in the first six weeks after assault.[4] These results, together with previous data demonstrating that (1) stress exposure results in the release of endogenous opioids[18, 26, 27, 43] and (2) stress-induced endogenous opioid release causes OIH[26, 46], support the hypothesis that endogenous OIH contributed to persistent MSP in the weeks after assault. Results from the present study of MVC survivors provides further support for the hypothesis that, among women trauma survivors experiencing substantial distress, endogenous OIH might contribute to persistent MSP in the weeks after trauma. In addition, these results suggest a specific mechanism by which an emotional response to a traumatic event (distress) may contribute to a specific biologic mechanism (endogenous opioid release) that increases MSP in the weeks after a trauma exposure. In the future, this information may be useful in helping to tailor secondary preventive interventions (e.g., low dose naloxone) for particular trauma survivor subgroups. The consistency of this finding among women experiencing substantial distress after both sexual assault and MVC suggests that this mechanism may contribute to MSP in the weeks after other trauma exposures as well. However, future experiments will be necessary in order to fully substantiate this possibility.

In contrast to the previous study of sexual assault survivors, in which all study participants were women with substantial peritraumatic distress, the present MVC cohort study provided the opportunity to evaluate the influence of A118G allele on MSP outcomes among men and among both distressed and non-distressed women. The modest effect of A118G among all women indicates that OIH has an effect on MSP symptoms in the weeks after trauma only among women with substantial peritraumatic distress. While not significant, point estimates in stratified analyses suggested that the effect of the G allele may be protective against pain in women and may be associated with augmented pain in men. Of note, when peritraumatic distress is added to the linear regression model for all individuals, a sex difference in the effect of A118G is still observed. Point estimates for men vs women are consistent with results from several previous studies. Fillingim et al found opposite effects of A118G on experimental heat pain among men and women, with the presence of a G allele associated with decreased pain in men and increased pain in women.[17] Similarly, Olsen et al found opposite effects on pain outcomes after low back surgery among men and women, with the presence of a G allele associated with decreased pain in men and increased pain in women.[36] In contrast to these studies, Lotsch et al found that healthy men and women volunteers with one or more copies of the G allele at A118G experienced decreased cortical activation following acute experimental pain stimuli[28]

Reasons for the varying direction of sex-dependent effects of A118G across studies remain poorly understood. Regarding varied findings, one contributing factor is likely the varied nature of the trauma/stress exposures and the timing of the outcome assessment across

studies. Increasing evidence indicates that both the nature of the stress or pain exposure and the timing of outcome assessments impact pain mechanisms.[23, 30] Ethnic differences in study populations also likely contribute to differences across study settings.[5, 21]

Within-study sex differences in the effect of A118G variants on pain outcomes are also poorly understood, and may be due to fundamental sex differences in neural circuits in the brain and spinal cord mediating stress-induced analgesia and opioid responses (reviewed in[32]). For example, at equal levels of pain intensity, men and women have been shown to differ in the magnitude and direction of response to μ-opioid system activation in distinct brain nuclei,[50] and female rats have been shown to exhibit more pronounced OIH in response to morphine injection, which is thought to be mediated via melanocortin 1 receptor versus NMDA type glutamate receptor involvement in females versus males, respectively.[10, 20, 34] The effect of opioid systems on other critical stress systems, which also modulate neurosensory processing, such as the hypothalamic-pituitary-adrenal axis or inflammatory factors, has also been shown to be sex-dependent.[40, 47]

Secondary analyses in the present study suggest that the protective effect of a G allele at A118G was greater among those with the highest levels of pre-MVC pain. These results are consistent with the findings of Rivat et al, who found that in rats that are pain experienced stress induces hyperalgesia, not analgesia, through an NMDA-dependent pronociceptive mechanism.[43] Together these data suggest that prior life experiences play a substantial role in shaping pain responses to stress, and that opioid systems may contribute to this phenomenon.

As we have previously reported, we observed significant associations between baseline income and education levels at the time of trauma and worse pain outcomes after MVC,[31, 48] with lower income and education generally associated with worse pain outcomes. These findings are consistent with those of other studies,[1, 16] and demonstrate the influence of sociodemographic characteristics on pain outcomes following trauma exposure.

Several limitations should be considered when interpreting our study results. First, some women in the study sample received exogenous opioids, and this could have contributed to our study results. However, when individuals who received opioids in the emergency department (n = 284) and/or in the weeks after MVC (n = 168) were removed from analyses, effect size differences for the presence of one or more copies of the G allele did not change (data not shown). Similarly, in the previously reported sexual assault study, the effect of A118G on pain outcomes did not change when women receiving exogenous opioids were removed from analyses.[4] Another limitation of our study is our small sample size and evaluation of a single polymorphism. Previously, we showed association between *FKBP5* and *COMT* genes with 6 week pain outcomes; when adding the tagging alleles from these previous studies to the current models for A118G, the associations remain significant (data not shown). In addition, we were also not able to assess the effects of ethnicity on our findings since only European American individuals were enrolled in this study. Finally, another limitation of this study is that, consistent with other studies enrolling trauma survivors[19, 44, 45] and the challenges of performing ethical studies of traumatized individuals

in the acute aftermath of trauma, this study did not enroll all eligible study participants. The generalizability of our results to those who declined enrollment is not known.

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Perspective

These results suggest a sex-dependent mechanism by which an emotional response to trauma (distress) contributes to a biologic mechanism (endogenous opioid release) that increases MSP in the weeks after stress exposure. These results also support the hypothesis that endogenous opioids influence pain outcomes differently in men and women.

Highlights

- We examined the effect of *OPRM1* A118G on persistent pain following MVC stress
- Women with a G allele and distress at the time of MVC had reduced pain at 6 weeks
- Men with a G allele had increased pain 6 weeks following MVC
- Results show a sex dependent effect of A118G on pain development following stress
- Effect of *OPRM1* allele on pain after stress suggests endogenous OIH mechanism

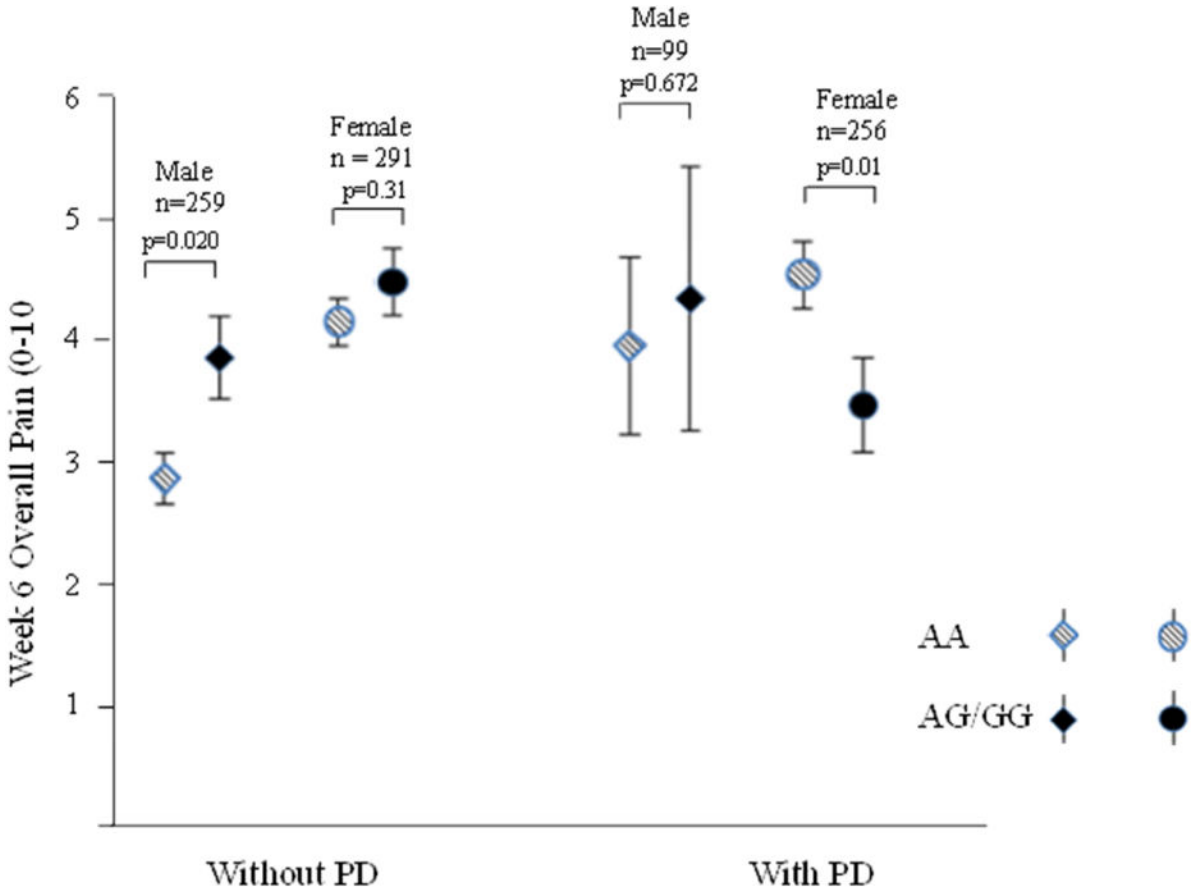

Figure 1.

Mean overall pain levels associated with AA versus AG/GG genotypes at OPRM1 allele A118G 6 weeks after MVC in men and women with and without peritraumatic distress. Pain levels were measured on a scale of 0–10 (NRS). Males = diamonds and females = circles. P values were calculated via multivariate analyses adjusted for site, age, education, income, pain prior to MVC and pain at the time of initial evaluation. Error bars represent the standard error of the mean.

Table 1

Baseline characteristics of study participants

Characteristic	All (n=948)	Female (575, 61%)	Male (373, 39%)
Age (mean, SD)	35 (13)	35 (13)	35 (13)
Education (n, %)			
Secondary school	283 (30)	150 (26)	133 (36)
Some college	312 (33)	172 (30)	140 (38)
College graduate/post-graduate	351 (37)	252 (44)	99 (27)
Income (n, %)			
$0–$19,999	117 (12)	84 (16)	33 (10)
$20,000–$39,999	176 (19)	115 (22)	61 (19)
$40,000–$79,999	277 (29)	178 (35)	99 (30)
$80,000 or higher	273 (29)	139 (36)	131 (41)
Collision type (n, %)			
Front end	439 (46)	262 (46)	177 (48)
Rear end	340 (36)	206 (36)	134 (36)
Relationship (n, %)			
No serious relationship	297 (31)	178 (31)	119 (32)
In a serious relationship	267 (29)	171 (30)	96 (26)
Married	371 (39)	217 (38)	154 (42)
Peritraumatic Distress (n, %)	355 (37)	256 (47)	99 (28)
Genotype (n, %)			
AA	732 (77)	442 (77)	290 (78)
AG	197 (21)	123 (21)	74 (20)
GG	17 (2)	9 (2)	8 (2)

Table 2

Linear regression model results demonstrating a main effect of *OPMR1* allele A118G on overall pain severity six weeks after motor vehicle collision (MVC) and an A118G-sex interaction (n = 859)

Independent variable[a]	Beta	SE	P
A118G (presence or absence of G allele)	0.815	0.358	0.023
Female Sex	0.857	0.222	<0.001
A118G allele * Sex	−1.059	0.446	0.017
Age	0.023	0.007	0.001
Education	−0.249	0.072	0.001
Income	−0.164	0.054	0.003
Pain at the time of initial evaluation	0.046	0.004	<0.001
Pain prior to MVC	0.025	0.041	0.549

[a] Study site was also included in model as a categorical variable

Table 3

General linear models examining the relationship of *OPRM1* allele A118G on overall pain severity six weeks after motor vehicle collision (MVC) among all men and women and among men and women with substantial peritraumatic distress after MVC

Independent variable[a]	Beta	SE	P
In all women (n = 575)			
A118G allele	−0.264	0.268	0.324
Age	0.013	0.009	0.146
Education	−0.291	0.091	0.001
Income	−0.185	0.068	0.007
Pain at the time of initial evaluation	0.044	0.006	0.000
Pain prior to MVC	0.014	0.051	0.780
In women with peritraumatic distress (n = 256)			
A118G allele	−0.925	0.375	0.014
Age	0.022	0.013	0.100
Education	−0.170	0.135	0.205
Income	−0.230	0.102	0.024
Pain at the time of initial evaluation	0.041	0.008	<0.001
Pain prior to MVC	0.035	0.070	0.621
In men (n = 373)			
A118G allele	0.827	0.352	0.019
Age	0.041	0.011	0.000
Education	−0.197	0.115	0.086
Income	−0.121	0.090	0.179
Pain at the time of initial evaluation	0.049	0.007	<0.001
Pain prior to MVC	0.066	0.070	0.347
In men with peritraumatic distress (n = 99)			
A118G allele	0.340	0.802	0.672
Age	0.070	0.025	0.006
Education	0.115	0.242	0.636
Income	−0.255	0.169	0.132
Pain at the time of initial evaluation	0.039	0.010	<0.001
Pain prior to MVC	0.041	0.117	0.728

[a] Study site was also included in model as a categorical variable

Table 4

a. General linear model examining the relationship of *OPRM1* allele A118G with overall pain intensity 6 weeks following MVC in women reporting high levels of pain prior to MVC

Independent variable[a]	Beta	SE	P
In women with high pain prior to MVC[b] (n = 97)			
A118G allele	−1.727	0.507	0.001
Age	0.017	0.017	0.309
Education	−0.182	0.168	0.276
Income	−0.565	−0.840	<0.001
Pain at the time of initial evaluation	0.226	0.093	0.015

b. Linear regression model examining the relationship of *OPRM1* allele A118G with overall pain intensity 6 weeks following MVC in men reporting high levels of pain prior to MVC

Independent variable[a]	Beta	SE	P
In men with high pain prior to MVC[b] (n = 50)			
A118G allele	1.742	0.914	0.057
Age	0.065	0.031	0.034
Education	−0.530	−0..269	0.049
Income	0.100	0.224	0.656
Pain at the time of initial evaluation	0.646	0.133	<0.001

[a] Study site was also included in model as a categorical variable

[b] High pain prior to MVC was defined by a score of 10 or more (top quartile of individuals)