μ-Opioid Receptor Gene A118G Polymorphism Predicts Pain Recovery After Sexual Assault

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Abstract: Pain is common after sexual assault (SA), but etiology of pain symptoms after SA is unknown. Preclinical studies suggest that the release of endogenous opioids during stress produces delayed-onset hyperalgesia. In human studies, individuals with 1 or more G alleles at the μ-opioid receptor functional single nucleotide polymorphism A118G have been shown to have a reduced response to opioids. We hypothesized that if opioid-mediated hyperalgesia contributes to pain after SA, women SA survivors with 1 or more G alleles at A118G would experience reduced postassault pain. Among 52 European American women SA survivors presenting for care within 48 hours of SA, those with a G allele (12/52, 23%) experienced less severe pain (F[1,39] = 11.55, P = .002) and a reduced extent of pain (F[1,41] = 11.01, P = .002) during the 6 weeks after SA. These associations between the presence of 1 or more G alleles and reduced pain severity and reduced pain extent after SA remained significant in multivariable models controlling for age, income, education, reported pain prior to assault, and pain at the time of initial evaluation.

Perspective: These results suggest that endogenous opioid-mediated hyperalgesia may contribute to pain symptoms after sexual assault. Further studies examining mechanisms mediating the development of pain after sexual assault, and the potential influence of opioid-mediated hyperalgesia, are needed.

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One in five U.S. women experience sexual assault (SA) during their lifetime.9 Cross-sectional studies of women SA survivors evaluated months or years after assault indicate that chronic musculoskeletal pain is commonly reported in this population9,16,20,23,27,31,39,42 and is associated with substantial suffering11,16,26,31,39,42 and diminished health.11,16,17,20,26,27,31,39,42 In a recent prospective study (n = 83), we reported that more than half of SA survivors experience severe pain in 4 or more body regions during the week after sexual assault. Among women conscious throughout the assault, the majority of body areas of pain were not areas in which trauma was reported.32 These data, together with individual case histories from women who reported no physical trauma but developed severe pain across multiple body regions,32 suggest that stress-induced hyperalgesia may play an important role in development of pain after sexual assault. Profoundly stressful events such as SA result in the release of endogenous opioids.41 A number of studies in both animals and humans have shown that μ-opioid...
receptor agonists produce a bimodal response: an initial brief period of analgesia followed by a delayed onset of more persistent and widespread hyperalgesia. Animal studies have shown that widespread stress-induced hyperalgesia can be diminished or prevented by the administration of the μ-opioid antagonist naltrexone. These data suggest that μ-opioid receptor activation plays an important role in the development of stress-induced hyperalgesia.

A number of functional genetic variants have been identified within the gene coding for the μ-opioid receptor. The most common and well-studied variant is the single nucleotide polymorphism (SNP) A118G. The G allele results in reduced receptor transcription and response to μ-opioid receptor binding. Individuals with 1 or more G alleles have been found to have a reduced analgesic response to opioids.

We hypothesized that μ-opioid receptor activation influences the development of stress-induced hyperalgesia after sexual assault. If this is the case, then based on the above evidence that individuals with 1 or more copies of the G allele at A118G have a reduced response to opioids, we hypothesized that women SA survivors with 1 or more copies of the G allele at A118G would experience reduced μ-opioid receptor-mediated hyperalgesia and therefore less pain during the initial weeks after sexual assault.

Methods

Participant Eligibility Criteria and Study Sites

Women SA survivors 18 years of age or older who presented for medical care (Sexual Assault Nurse Examiner [SANE] evaluation) within 48 hours of SA were recruited for the study. Women unable to give informed consent (eg, due to intoxication) were excluded, as were women who lived with their assailant, were hospitalized, were prisoners, were pregnant, did not have a telephone, and/or did not live within driving distance for the 1-week follow-up interview. Ten SANE programs (Mercy Medical Center, Baltimore, MD; University of North Carolina, Chapel Hill, NC; Cone Health System, Greensboro, NC; Inova Fairfax Hospital, Falls Church, VA; Sentara Norfolk Hospital, Norfolk, VA; Carolinas Medical Center, Charlotte, NC; Palmetto Health Alliance, Columbia, SC; Wake Forest Baptist Medical Center, Winston-Salem, NC; Forsyth Medical Center, Winston-Salem, NC; Mission Health System, Asheville, NC) participated in the study. These programs care for women SA survivors from diverse environments, from inner city Baltimore to rural Appalachia. Institutional review board approval was obtained at all study sites.

Study Procedures and Measures

When a potentially eligible SA survivor presented for care, the nurse provider notified an on call research nurse via a 24-hour study cell phone. The research nurse then came to the study site, introduced herself to the SA survivor, and asked for consent to 1) telephone the survivor in several days to assess her willingness to participate in a 1-week follow-up interview; and 2) perform a brief questionnaire evaluation assessing current pain intensity in each of 8 body regions (head and face, neck, breast, arms, abdomen, back, genital and pelvic, and legs). Pain intensity was assessed in each body region using a verbal 0 to 10 numeric rating scale (NRS), as this scale has been validated against the visual analog scale for acute pain measurement and has advantages in acute care settings. In recognition of the fact that study consent was obtained at the time of SANE care, a time of great duress and vulnerability, and that safety data regarding this type of research protocol are not available, women were informed that pain questionnaire data would only be retained/used if they also subsequently consented to take part in subsequent follow-up interview evaluations.

SA survivors contacted by telephone and consenting to a 1-week, in-person follow-up interview received a reassessment of current pain symptoms using the methods described above. Following the assessment of current pain symptoms, pain symptoms during the week prior to assault were also evaluated using these same methods. Acute stress disorder (ASD) symptoms (ASD Interview) were also assessed at the 1-week interview; a cutoff score of >27 defined ASD. A saliva sample was also obtained (Oragene DNA Self-Collection Kits; Ottawa, ON, Canada) for DNA analysis at the 1-week interview.

Women completing a 1-week follow-up evaluation were subsequently contacted by telephone to assess their willingness to complete a 6-week follow-up evaluation. Women consenting to a 6-week follow-up evaluation received a reassessment of current pain symptoms using the above methods. Posttraumatic stress disorder (PTSD) symptoms (PTSD Symptom Scale–Interview (PSS-I)) were also assessed at 6-week follow-up; PTSD was defined using PSS-1 criteria. Detailed SA history, patient physical examination information, and information regarding medication prescribed at the time of initial SANE evaluation were obtained from SANE/medical records. Demographic information (age) was obtained from the medical record and via 1-week interview (eg, household income, education level). Women were compensated $50 for completing the 1-week interview and $60 for completing the 6-week interview.

Genotyping

Genotyping at rs1799971 was performed using the Sequenom platform. Genotyping was repeated on a 10% random sample of participants. There was 100% call agreement between original and repeat genotyping.

Statistical Analysis

Pain severity distributions and mean number of regions of moderate or severe pain (defined by a pain score of 4 or greater on a 0–10 NRS) among women SA survivors across time points were calculated using standard descriptive statistics. Student t-test was used to compare number of body regions with moderate or severe pain by genotype and overall pain scores by genotype at each
Results

Study Enrollment and Genotyping

Eighty-four women SA survivors enrolled in the study. Seventy-five of these women (89%) completed a 6-week follow-up. All study participants provided saliva DNA samples; the call rate at A118G was 100%. However, the A118G SNP was genotyped on a panel containing several hundred SNPs, and 4 saliva samples failed due to low call rates (<95%) across all panel SNPs and were excluded.

According to data from the HapMap database and a previous large population-based study performed by the study team, the prevalence of the G allele at A118G is ~25 to 30% among European Americans and ~5 to 7% among African Americans. Among women SA survivors in the study sample, the G allele was present in 12/52 (23%) of European Americans and 0/28 (0%) of African Americans. Because no African American women had a G allele at A118G, and because evidence suggests that the influence of a genetic variant may differ between ethnic groups (including A118G), subsequent analyses were limited to European Americans with valid genetic data. These women comprised the study sample.

Characteristics of the Study Sample

Characteristics of European American SA survivors who comprised the study sample are shown in Table 1. Most women were less than 30 years of age (37/52, 71%) and had some education or training past high school (40/51, 78%). Median annual family income of women SA survivors in the study sample was $20,000 to $39,999. Most women did not have children (34/51, 67%). Characteristics of women with and without 1 or more G alleles at A118G were similar (Table 1). Among European American women who recalled at least some of the assault (28/51, 55%), the great majority (26/28, 93%) experienced penile-vaginal penetration. More than half of women (15/28, 54%) experienced multiple forms of assault (eg, penile-anal, penile-oral, oral-vaginal). Most women (19/28, 68%) were assaulted by an individual who was not a stranger. Eighteen women (35%) had no identifiable physical injury at the time of SANE examination.

Only 5/52 (10%) European American women received an opioid pain medication at the time of emergency department (ED) evaluation (2 mg of dilaudid, 1 mg of dilaudid, 2 tablets of oxycodone/acetaminophen, 1 tablet of 5/325 oxycodone/acetaminophen, 100 µg of fentanyl, respectively). An opioid was received at the time of ED evaluation by 4/40 (10%) of women with no copies of the G allele at A118G, and 1/12 (8%) of women with 1 or more copies of the G allele. No woman received an opioid medication prescription at the time of discharge from the ED. At 6-week follow-up, 3/44 (7%) of women reported taking 1 or more doses of prescription opioid medication after discharge from the ED. Use of prescription opioids was reported by 3/35 (9%) of women with no copies of the G allele at A118G, and 0/9 (0%) of women with 1 or more copies of the G allele.

Pain Severity and Extent During the First 6 Weeks After SA

The extent and severity of pain during the initial 6 weeks after SA are shown in Table 2. The great majority of women SA survivors experienced moderate or severe pain during the week after assault, and more than 40% of the women continued to report moderate or severe pain in 1 or more body regions 6 weeks after assault. Women SA survivors in the study sample experienced an average of more than 3 regions of moderate or severe pain during the week after assault, and an average of more than 2 regions of moderate or severe pain 6 weeks after assault.

Association Between A118G Genotype and Pain Severity After SA

On repeated measures analysis, women SA survivors with 1 or more G alleles at A118G had decreased pain severity during the initial 6 weeks after SA (F[1, 39] = 11.55, P = .002) (Fig 1). This association persisted after adjusting
for age, income, education, prior overall pain, and overall pain at the time of initial evaluation (F [1,21] = 18.12, P = .0004). When overall pain severity scores of SA survivors with and without 1 or more G alleles were compared at individual time points, there was no difference in pain scores of women SA survivors with and without 1 or more G alleles reported during the week prior to assault (1.4 [2.0] versus .91 [1.0], P = .443) or at the time of initial presentation (7.0 [3.0] versus 6.6 [2.6], P = .659). However, women with 1 or more G alleles at A118G had significantly lower overall pain scores 1 week after SA (2.4 [2.2] versus 5.4 [2.8], P = .002) and 6 weeks after SA (1.0 [1.0] versus 3.3 [2.8], P = .018). Each of these associations remained significant when women reporting the use of opioids were dropped from study analyses.

**Association Between A118G Genotype and Pain Extent After SA**

On repeated measures analysis, women SA survivors with 1 or more G alleles at A118G reported significantly fewer body regions with moderate or severe pain during the initial 6 weeks after SA (F [1,41] = 11.01, P = .002) (Fig 2). This association persisted after controlling for age, income, education, prior number of body regions with moderate or severe pain, and number of body regions with moderate or severe pain at the time of initial evaluation (F [1,23] = 6.57, P = .018). When overall pain severity scores of SA survivors with and without 1 or more G alleles were compared at individual time points, there was no difference in the number of body regions with moderate or severe pain reported during the week prior to assault (.3 [.6] versus .9 [.5], P = .145) or at the time of initial presentation for care after SA (2.5 [1.7] versus 2.4 [1.8], P = .864). However, women with 1 or more G alleles reported a significantly lower number of body regions with moderate or severe pain 1 week after SA (.6 [.90] versus 2.5 [2.0], P = .002) and 6 weeks after SA (.1 [.3] versus 2.0 [2.2], P = .014). Each of these associations remained significant when women reporting the use of opioids were dropped from study analyses.

**Figure 1.** Pain scores across time points among women SA survivors with 1 or more copies of the G allele (+G) or no copies of the G allele (AA) at A118G. Overall pain scores were assessed at each time point using a 0 to 10 NRS. (Pain at the time of presentation was assessed using worst pain score, as overall pain score was not obtained at this time point.) Asterisks indicate P < .05 for comparison of pain scores at time point.

**Figure 2.** Number of body regions with moderate or severe pain across time points among women SA survivors with 1 or more copies of the G allele (+G) or no copies of the G allele (AA) at A118G. Moderate or severe pain was defined as pain >= 4 on a 0 to 10 NRS. Asterisks indicate P < .05 for comparison of pain scores at time point.

**Table 2. Pain Severity and Extent Among Women SA Survivors (N = 52)**

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>REPORTED DURING WEEK PRIOR TO ASSAULT</th>
<th>1 WEEK AFTER PRESENTATION</th>
<th>6 WEEKS AFTER ASSAULT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain severity* (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No pain</td>
<td>25 (49)</td>
<td>1 (2)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Mild pain</td>
<td>21 (41)</td>
<td>8 (15)</td>
<td>13 (25)</td>
</tr>
<tr>
<td>Moderate pain</td>
<td>4 (8)</td>
<td>12 (22)</td>
<td>17 (33)</td>
</tr>
<tr>
<td>Severe pain</td>
<td>1 (2)</td>
<td>33 (61)</td>
<td>17 (33)</td>
</tr>
<tr>
<td>Regions of moderate or severe pain (mean, SD)</td>
<td>.8 (1.4)</td>
<td>2.4 (1.7)</td>
<td>2.1 (2.0)</td>
</tr>
</tbody>
</table>

*Based on overall NRS pain scores. No pain = NRS 0; mild pain = NRS 1 to 3; moderate pain = NRS 4 to 6; severe pain = NRS 7 to 10. Worst pain score used at time of presentation, as overall pain not assessed at that time point.
Discussion

Our study results suggest that endogenous μ-opioid-mediated hyperalgesia may contribute to the development of pain symptoms among women SA survivors. The importance of μ-opioid-mediated hyperalgesia to postassault pain symptoms is suggested by the fact that women in our sample with a genetic variant resulting in a reduced response to μ-opioid receptor binding23,45 (1 or more G alleles at A118G) experienced a substantial and clinically relevant13 reduction in pain severity 1 and 6 weeks after assault. Women with 1 or more G alleles at A118G also experienced a reduction in the number of body regions with moderate or severe pain. The timing of the reduction in pain experienced by women with 1 or more G alleles (no difference in pain reported prior to assault or at the time of initial presentation within 48 hours of assault, but reduced pain at 1 and 6 weeks) is consistent with the delayed onset of opioid-induced hyperalgesia observed in animal studies.1,6-8,19,25,29 While not significant, women with 1 or more G alleles at A118G tended to have higher pain scores at the time of initial presentation. This finding suggests that women with 1 or more G alleles at A118G may experience both a reduced initial analgesic response to endogenous opioids and a reduction in delayed-onset, more long-lasting opioid-mediated hyperalgesia.

Genetic analyses among our sample were limited to European American SA survivors only; stratified analyses using African American women were not possible because no African American women in our relatively small study sample had a G allele at A118G. As noted above, the decreased G allele prevalence in African Americans versus European Americans in our study sample is consistent with previous data from other cohorts.4 If individuals with a G allele experience a reduction in stress-induced hyperalgesia mediated by endogenous opioids, then the reduced G allele prevalence among African Americans may be 1 factor contributing to the increased burden of pain experienced by African Americans.18

While women with a G allele at A118G had lower ASD symptom severity and PTSD symptom severity scores than women without a G allele, differences were modest and not statistically significant. This lack of difference may be due to a greater influence of the A118G polymorphism on pain outcomes relative to these psychological outcomes in the weeks after sexual assault, and/or to the very high ASD and PTSD symptom scores among study participants. These high scores, and a relative lack of score variability in the early weeks after sexual assault, would result in reduced power to detect a difference in these outcomes.

Several limitations should be considered when interpreting our study results. Most importantly, the relatively small size of our study sample increases the likelihood of a false positive result (type I error). However, we believe that from a Bayesian viewpoint, our evaluation of a single well-studied functional polymorphism and our assessment of a single hypothesis well supported by preclinical data reduce this risk. Certainly, our findings require replication in other studies of SA survivors, and in other clinical samples of individuals exposed to less extreme forms of traumatic stress. In addition, some women in the study sample received exogenous opioids. However, opioids were received by only a small proportion of study participants. (In fact, we have provided our study results to participating study sites, and this has resulted in a change in care protocols at a number of sites to increase pain treatment for SA survivors who present for care with moderate or severe pain.) In addition, study results remained significant when women who had received exogenous opioids were removed from analyses. Another limitation of our study is that our small sample size does not allow us to evaluate the influence of the AG versus GG genotype in our sample (ie, homozygous versus heterozygous). Finally, another limitation of this study is that, consistent with other studies enrolling trauma survivors,24,36,38 and the challenges of performing ethical studies of severely traumatized individuals in the acute aftermath of trauma, this study enrolled only a minority of potentially eligible women. The generalizability of our results to women who declined enrollment is not known.

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References


