Published in final edited form as:
J Burn Care Res. 2012 ; 33(4): 518–523. doi:10.1097/BCR.0b013e31823746ed.

Catechol-*O*-methyltransferase genotype predicts pain severity in hospitalized burn patients

Danielle C. Orrey, BA,
Department of Anesthesiology and the TRYUMPH Research Program, University of North Carolina, Chapel Hill

Andrey V. Bortsov, MD, PhD,
Department of Anesthesiology and the TRYUMPH Research Program, University of North Carolina, Chapel Hill

Janelle M. Hoskins, PharmD,
Molecular Genomics Facility, University of North Carolina, Chapel Hill

Jeffrey W. Shupp, MD,
The Burn Center, Department of Surgery, Washington Hospital Center

Samuel W. Jones, MD,
Jaycee Burn Center, University of North Carolina, Chapel Hill

Corresponding Author: Danielle C. Orrey, TRYUMPH Research Program, The University of North Carolina, 334 Emergency Room Drive, Medical Wing C, CB #7010, Chapel Hill, NC 27599-7455, Phone: 919-966-7315, FAX: 919-966-7193, dorrey@aims.unc.edu.

Role: Danielle C. Orrey: This author helped conduct the study, analyze the data, and write the manuscript
Role: Andrey V. Bortsov: This author helped analyze the data and write the manuscript
Role: Janelle M. Hoskins: This author helped write the manuscript
Role: Jeffrey W. Shupp: This author helped conduct the study and write the manuscript
Role: Samuel W. Jones: This author helped conduct the study and write the manuscript
Role: Bryan J. Cicuto: This author helped conduct the study and write the manuscript
Role: James Hwang: This author helped conduct the study and write the manuscript
Role: Marion H. Jordan: This author helped conduct the study and write the manuscript
Role: James H. Holmes: This author helped conduct the study and write the manuscript
Role: Linwood R. Haith: This author helped conduct the study and write the manuscript
Role: Brandon M. Roane: This author helped conduct the study and write the manuscript
Role: Luda Diatchenko: This author helped design the study and write the manuscript
Role: Bruce A. Cairns: This author helped conduct the study and write the manuscript
Role: Samuel A. McLean: This author helped design the study, conduct the study, analyze the data, and write the manuscript

Conflicts: Danielle C. Orrey reported no conflicts of interest
Conflicts: Andrey V. Bortsov reported no conflicts of interest
Conflicts: Janelle M. Hoskins reported no conflicts of interest
Conflicts: Jeffrey W. Shupp reported no conflicts of interest
Conflicts: Samuel W. Jones reported no conflicts of interest
Conflicts: Bryan J. Cicuto received honoraria from Baxter ARTISS [Fibrin Sealant (Human)] and from the EXIGO Management Consultants Professional Opinion Survey: Wound Care/Burn Care, and received research funding from Ethicon Education Grants
Conflicts: James Hwang reported no conflicts of interest
Conflicts: Marion H. Jordan reported no conflicts of interest
Conflicts: James H. Holmes reported no conflicts of interest
Conflicts: Linwood R. Haith reported no conflicts of interest
Conflicts: Brandon M. Roane reported no conflicts of interest
Conflicts: Luda Diatchenko consulted for Algynomics, has equity interest in Algynomics, and reported a conflict of interest with Algynomics
Conflicts: Bruce A. Cairns reported no conflicts of interest
Conflicts: Samuel A. McLean reported no conflicts of interest

Institutions: The University of North Carolina at Chapel Hill, Washington Hospital Center, Wake Forest Baptist Medical Center, Crozer Chester Medical Center

Bryan J. Cicuto, DO,
Jaycee Burn Center, The University of North Carolina, Chapel Hill

James Hwang, MD,
Jaycee Burn Center, University of North Carolina, Chapel Hill

Marion H. Jordan, MD,
The Burn Center, Department of Surgery, Washington Hospital Center

James H. Holmes, MD,
Wake Forest University Baptist Burn Center

Linwood R. Haith, MD,
Nathan Speare Regional Burn Treatment Center, Crozer Chester Medical Center

Brandon M. Roane, BS,
Department of Anesthesiology, and the TRYUMPH Research Program, University of North Carolina, Chapel Hill

Luda Diatchenko, MD, PhD,
Center for Neurosensory Disorders, University of North Carolina, Chapel Hill

Bruce A. Cairns, MD, and
Jaycee Burn Center, University of North Carolina, Chapel Hill

Samuel A. McLean, MD, MPH
Department of Anesthesiology, and the TRYUMPH Research Program, University of North Carolina, Chapel Hill

Andrey V. Bortsov: abortsov@aims.unc.edu; Janelle M. Hoskins: jmhoskin@email.unc.edu; Jeffrey W. Shupp: Jeffrey.W.Shupp@medstar.net; Samuel W. Jones: samuel_jones@med.unc.edu; Bryan J. Cicuto: bryan_cicuto@med.unc.edu; James Hwang: james_hwang@med.unc.edu; Marion H. Jordan: Marion.H.Jordan@Medstar.net; James H. Holmes: jholmes@wfubmc.edu; Linwood R. Haith: linwood.haith@verizon.net; Brandon M. Roane: bmroane@gmail.com; Luda Diatchenko: lbdiatch@email.unc.edu; Bruce A. Cairns: bruce_cairns@med.unc.edu; Samuel A. McLean: smclean@aims.unc.edu

Abstract

Background—Increasing evidence suggests that stress system activation after burn injury may contribute to burn-related pain. If this is the case, then genetic variations influencing the function of important stress system components, such as the enzyme catechol-*O*-methyltransferase (COMT), may predict pain severity after thermal burn injury.

Methods—We evaluated the association between *COMT* genotype and pain intensity in 57 individuals hospitalized after thermal burn injury. Consenting participants at four burn centers were genotyped and completed daily 0-10 numeric rating scale pain assessments on two consecutive days including evaluation of waking, least, and worst pain. The association between *COMT* genotype and individual pain outcomes was calculated using a linear mixed model adjusting for sociodemographic and burn injury characteristics.

Results—Overall pain (combination of least, worst, and waking pain scores) was significantly higher in patients with a *COMT* pain vulnerable genotype (6.3 (.4) vs. 5.4 (.4), p=.037). Individuals with a *COMT* pain vulnerable genotype also had significantly higher “least pain” scores (3.8 (.5) vs. 2.6 (.4), p=.017) and significantly higher pain on awakening (6.8 (.5) vs. 5.3 (.4), p=.004). Differences in worst pain according to genotype group were not significant. *COMT* pain vulnerable genotype was a stronger predictor of overall pain severity than burn size, burn depth, or time from admission to pain interview assessment.

Conclusions—These findings suggest that genetic factors influencing stress system function may have an important influence on pain severity after burn injury. Further studies of genetic predictors of pain after burn injury are needed.

Keywords

catechol-*O*-methyltransferase; burn; pain; stress

Introduction

Despite major advances in burn care, most of the ~50,000 patients admitted to US burn centers each year[1] experience substantial pain during hospitalization.[2,3] It is often assumed that burn pain intensity is primarily determined by injury characteristics such as burn size and depth. However, available data indicate that burn characteristics are not strong predictors of burn-related pain.[4-6] This suggests that other, as yet unidentified factors may play an important role in determining the pain experience of burn patients. The identification of such factors may create new opportunities to improve burn care.

Increasing evidence suggests that stress response system activation after burn injury may contribute to burn-related pain. In addition to causing direct tissue damage, a burn injury is a potent stressor which activates the sympathetic nervous system and adrenomedullary hormonal system, resulting in the release of catecholamines.[7] Results of both animal and human studies have demonstrated that catecholamine levels influence pain sensitivity.[8-13] If this is the case, then genetic variations affecting catecholamine levels may predict individual variations in pain severity after burn injury.

One stress system component influencing catecholamine levels is the enzyme catechol-*O*-methyltransferase (COMT). COMT is the primary enzyme that metabolizes catecholamines, including epinephrine, norepinephrine, and dopamine.[14] Genetic variations in the *COMT* gene (*COMT* diplotype) influencing COMT enzyme function have been found to predict acute pain sensitivity in experimental settings.[15] In addition, classifying patients by *COMT* diplotype into those with or without a "*COMT* pain vulnerable genotype" has been shown to predict musculoskeletal pain severity and psychological distress after minor injury.[16] However, to our knowledge the potential contribution of genetic variations influencing the function of important stress system components such as *COMT* to pain after major injury has never been examined. In this study we examined the association between *COMT* pain vulnerable genotype and pain intensity among patients admitted to the hospital after thermal burn injury. We hypothesized that hospitalized burn patients with a *COMT* pain vulnerable genotype would experience increased pain in comparison to those without this genotype. In addition, we compared the strength of association between *COMT* genotype and acute burn pain with the strength of association between several commonly assessed burn injury characteristics and acute burn pain. Because of increasing evidence that individual neurobiology has an influence on pain outcomes comparable to/greater than injury severity,[16] we hypothesized that *COMT* genotype would have an influence on pain as great or greater than characteristics of the burn injury.

Methods

Patients presenting to four burn centers (Jaycee Burn Center, University of North Carolina, Chapel Hill, NC; The Burn Center, Washington Hospital Center, Washington, DC; Wake Forest University Baptist Burn Center, Wake Forest, NC; Nathan Speare Regional Burn Treatment Center, Upland, PA) within 72 hours of thermal burn injury between June 2009 to January 2011 were evaluated for study eligibility. Patients who were clinically unstable or

who had coincident non-burn injury were excluded, as were prisoners, pregnant patients, patients with intentional injury, patients with a psychotic disorder, non-English speaking patients, and patients with hepatic failure, renal failure, or a history of chronic opioid use (defined as ≥ 20mg/day of oxycodone or equivalent). Also, because patients in this observational study were subsequently to be evaluated for participation in a randomized controlled medication trial, patients with greater than 20% total body surface area (TBSA) burn, patients with an estimated hospital stay of <5 days or > 40 days, patients with greater than first-degree atrioventricular block, patients taking a β-adrenergic antagonist medication, and patients with asthma, diabetes, coronary artery disease, and congestive heart failure were also excluded. Patients were also excluded who in the opinion of the investigators would not provide reliable data. Local Institutional Review Board approval was obtained from all study site IRBs.

Eligible patients were approached by research staff for study participation within 48 hours of burn center admission. Written informed consent was obtained from all participants. Study participation included blood sample collection for genetic analysis and completion of daily pain symptom interviews on two consecutive days following enrollment. During each daily pain symptom interview, participants were asked to rate their worst pain, their least pain, and their average pain over the past 24-hours, as well as their pain upon waking. Each pain assessment was performed using a verbal 0-10 numeric rating scale (NRS), where '0' was defined to the patient as 'no pain' and '10'; as 'pain as severe as it could possibly be'. A verbal NRS was used because it has been validated as a substitute for the Visual Analogue Scale in acute care settings,[17] and because it does not rely on upper extremity use to make a precise mark on a scale. Daily pain symptom interviews which included the above assessments were performed on two consecutive days, beginning on the day of enrollment.

For study analyses, our initial intention was to combine the two ratings of daily average pain for each patient (one rating each day obtained on two consecutive days). However, as daily pain symptom interviews were being conducted, it was observed that patients sometimes provided an "average" pain rating greater than their worst reported pain or less than their least reported pain. These observations, together with the high degree of educational disadvantage in this population, lead us to appreciate that our study question ("Please rate your average pain during the last 24 hours…") was poorly designed for the study population and (due to misunderstanding) did not yield valid data. Because of this, instead of using average pain, we took advantage of the multiple different pain assessments available within each individual (waking, worst, and least pain on two consecutive days) and created a measure of overall pain burden using linear mixed modeling described below. This measure of overall pain was used as the primary outcome measure for all analyses. Mean scores for waking, worst, and least pain over two days were also obtained from this model.

Study participants received analgesics as per standard study site burn care; no changes were made to the pain treatment of study participants. Information regarding medications received during the two-day study period was extracted from the medical record. For each opioid analgesic medication, total dose received during the two-day study period was calculated and then multiplied by a conversion factor referenced to a 30 mg dose of morphine.[18] These doses were then summed to provide the total opioid dose (in morphine equivalents) received by the patient during the two-day study period. Benzodiazepine conversions were similarly calculated using a 10 mg diazepam reference.[19] Demographic information was obtained during the initial patient assessment via standardized questionnaire. Information regarding patient burn characteristics was obtained from the medical record.

Blood samples were obtained for genetic analysis using an EDTA Vacutainer collection tube (BD, Franklin Lakes, New Jersey, USA). DNA was purified from whole blood samples

using the QIAamp DNA Mini Kit (QIAGEN, Valencia, California, USA) on the QIAcube (QIAGEN), as per manufacturer's instructions. Genotyping was performed using a TaqMan Allelic Discrimination Assay for rs4818 on the Bio-Rad CFX96 Real-time PCR Detection System (Bio-Rad, Hercules, California, USA) at either the University of North Carolina (Chapel Hill, NC) or Washington Hospital Center (Washington, DC). Patient DNA samples were genotyped together with six HapMap CEU DNA samples (two of each genotype) and two “no template” control samples.

When multiple disease susceptibility variants occur in the same gene, the overall functional state of the gene may not be easily deduced from information regarding a single nucleotide polymorphism (SNP).[20] For this reason we used a haplotype-based approach to examining *COMT* variants. In a previous study, three haplotypes located in the central *COMT* locus accounted for approximately 96% of all haplotypes in this region and were associated with variations in pain sensitivity[15] and post traumatic pain.[16] One of these haplotypes, the “low pain sensitivity haplotype”, codes for high COMT enzyme activity and is associated with relatively low pain vulnerability (i.e. is protective against pain).[15] As in a previous study,[16] we defined patients with no copies of this low pain sensitivity haplotype as having a “*COMT* pain sensitive genotype”. Patients with a *COMT* pain sensitive genotype were identified by genotyping SNP rs4818, because approximately 95% of individuals with a CC genotype at rs4818 have a *COMT* pain sensitive genotype.[15]

Statistical analyses used linear mixed modeling to evaluate the association between *COMT* pain vulnerable genotype and pain outcomes. Six pain measurements (waking, worst, and least pain for day 1 and day 2) for each individual were entered into the model as a correlated outcome variable. The correlations between pain measurements within each individual were taken into account by specifying nested random effects for intercept. The measure of overall pain was obtained as an adjusted least square mean pain score incorporating waking, worst, and least pain for day 1 and day 2. Mean scores for waking, worst, and least pain over two days were also obtained from this model. Age, gender, TBSA, burn depth, and time from admission to pain assessment were considered as important covariates and included in the model. In addition, because the frequency of genetic variations can vary by ethnicity,[21] associations between *COMT* pain vulnerable genotype and pain outcomes were also adjusted for patient ethnicity (European American vs. African American/Other). All analyses were conducted using SAS (version 9.2, SAS Institute Inc., Cary, NC). P-values < .05 were defined as statistically significant.

Results

Seventy-six patients were screened and determined to be eligible for study participation. Fifty-seven (75%) of these patients consented to study participation. Among these patients, the average number of days between burn injury and burn center admission was .6 days (.9), and the average number of days between burn center admission and the beginning of the two-day pain assessment period was 1.4 days (.9). Patient characteristics are shown in Table 1. Most patients were young European American males with partial thickness burn that was ≤ 10% TBSA. Median family income reported by study participants was $40,000-$60,000.

During the two-day study period, 100% (57/57) of participants received opioid analgesics, 11% (6/57) received benzodiazepines, and 2% (1/57) received nonsteroidal anti-inflammatory drugs. Twenty-five (44%) participants had a *COMT* pain vulnerable genotype. Patients with a *COMT* pain vulnerable genotype received more opioid and benzodiazepine medications (mean morphine equivalent opioids 66.5±49.5 vs. 53.3±29.7, p=.247, mean diazepam equivalent benzodiazepines 0.6±1.9 vs. 0.4±1.8, p=.804), although these differences did not reach statistical significance.

Associations between *COMT* genotype and patient pain experiences are shown in Table 2. Despite receiving more opioid and benzodiazepine medication, individuals with a *COMT* pain vulnerable genotype had significantly higher "least pain" scores and experienced significantly higher pain on awakening. Overall pain (combination of least, worst, and waking pain scores) was also significantly higher in patients with a *COMT* pain vulnerable genotype. In contrast, no association was observed between *COMT* pain vulnerable genotype and worst pain. These associations remained significant when adjusted for total burn size, full thickness burn size, age, gender, ethnicity, and time from admission to study assessment (Table 2).

Associations between selected patient characteristics and overall pain score are shown in Table 3. Age, gender, total burn size, full thickness burn size, and type of thermal burn had little influence on overall pain severity in our sample. Time from admission to pain assessment was associated with overall pain severity at the trend level. The strength of association between *COMT* pain vulnerable genotype and overall pain score exceeded that of any other individual or burn characteristics assessed.

Discussion

In our sample, *COMT* pain vulnerable genotype predicted pain severity upon waking and the least amount of pain that a burn patient experienced during a 24 hour period. In contrast, no association was observed between *COMT* pain vulnerable genotype and the worst pain that a burn patient experienced during a 24 hour period. This is likely due to a ceiling effect, as ~85% of patients reported a worst pain score ≥7. The presence or absence of a *COMT* pain vulnerable genotype was a stronger predictor of overall pain severity (combination of least, waking, and worst pain) in the early aftermath of burn injury than type of thermal burn, size or depth of burn, or time from admission to pain assessment. Patients in the sample with more severe pain received more opioid analgesics and more benzodiazepines, indicating that increased pain scores were not the result of reduced pain medication treatment.

While *COMT* pain vulnerable genotype influenced pain experiences after burn injury, it is important that *COMT* genotype not be viewed as "the genetic determinant" of pain intensity after burn injury. Indeed, the amount of variation in pain associated with the specific risk genotype (genetic variant) assessed in this study is relatively modest. It is also important to appreciate that the haplotypes used to define the genetic variant in this study are just a few of a number of different genetic factors that may influence the function of the COMT enzyme,[22,23] and that the COMT enzyme in turn is just one of a great many biologic components of catecholaminergic pathways. The primary utility of this preliminary study is to suggest the potential value using genetic variants influencing components of biological pathways related to catecholamines (and stress systems more broadly) to determine the biologic pathways/mechanisms which most strongly influence post-burn pain.

This study identifies a specific link between individual variation in a genetic variant influencing catecholamine metabolism (*COMT* pain vulnerable genotype) and pain after burn injury. In the present sample, this genetic variant had more influence on burn pain than burn injury characteristics. This finding is encouraging, as it suggests that novel treatments which target relevant biologic pathways related to stress may have a substantial influence on patient outcomes, even if the characteristics of the burn injury itself are immutable. This is important, because burn-related pain is a major cause of morbidity among burn injury survivors.[24]

When interpreting our study results, several limitations should be considered. First, our study included only thermal burn patients with TBSA burns ≤ 20%, and most patients in our sample had burns that were less than 10% TBSA. However, such burn injuries constitute the great majority (>86%) of admissions to major burn centers.[25] The generalizability of our findings to patients with larger burns or substantial third degree burns is unknown. Perhaps more importantly, because patients in this observational study were subsequently to be evaluated for participation in a randomized controlled medication trial, patients with greater than first-degree atrioventricular block, patients taking a β-adrenergic antagonist medication, and patients with asthma, diabetes, coronary artery disease, and congestive heart failure were also excluded. Therefore the generalizability of study findings to these patient groups cannot be assessed. Also, while our conclusions are valid regarding the relative influence of *COMT* genotype vs. burn characteristics on burn-related pain in our sample, our results should not be interpreted as evidence that other burn characteristics do not influence pain. This is because our sample was small, and did not include the full range of burn injuries. Finally, as described in the methods section, we erred when we assumed that patients would be consistently familiar with the term “average”. Because of this, our overall pain score combined waking pain, least pain, and worst pain, and actual differences regarding the average, or typical, pain experiences of burn patients according to *COMT* genotype are unknown. To prevent this error, future pain studies performed in burn centers should avoid asking patients about their “average pain” (using instead pain “most of the time”, etc).

Acknowledgments

The authors would like to sincerely thank all research participants and burn unit staff for their time and contributions to the outcomes in this manuscript.

Funding: This project was supported by Award Number UL1RR025747 from the National Center for Research Resources, the NC Jaycee Burn Center Fund, the Firefighters Research Fund, the DC Firefighters Burn Foundation, and UNC Institutional Resources

References

1. LaBorde P. Burn epidemiology: the patient, the nation, the statistics, and the data resources. Critical Care Nursing Clinics of North America. 2004; 16:13–25. [PubMed: 15062410]
2. Perry S, Heidrich G, Ramos E. Assessment of Pain by Burn Patients. Journal of Burn Care & Research. 1981; 2:322–6.
3. Summer GJ, Puntillo KA, Miaskowski C, Green PG, Levine JD. Burn Injury Pain: The Continuing Challenge. The Journal of Pain. 2007; 8:533–48. [PubMed: 17434800]
4. Choiniere M, Melzack R, Rondeau J, Girard N, Paquin MJ. The pain of burns: characteristics and correlates. J Trauma. 1989; 29:1531–9. [PubMed: 2585565]
5. Difede J, Jaffe AB, Musngi G, Perry S, Yurt R. Determinants of pain expression in hospitalized burn patients. Pain. 1997; 72:245–51. [PubMed: 9272809]
6. Richardson P, Mustard L. The management of pain in the burns unit. Burns. 2009; 35:921–36. [PubMed: 19505764]
7. Ballard-Croft C, Maass DL, Sikes P, White J, Horton J. Activation of stress-responsive pathways by the sympathetic nervous system in burn trauma. Shock. 2002; 18:38–45. [PubMed: 12095132]
8. Khasar SG, Green PG, Miao FJ, Levine JD. Vagal modulation of nociception is mediated by adrenomedullary epinephrine in the rat. Eur J Neurosci. 2003; 17:909–15. [PubMed: 12603283]
9. Khasar SG, McCarter G, Levine JD. Epinephrine produces a beta-adrenergic receptor-mediated mechanical hyperalgesia and in vitro sensitization of rat nociceptors. J Neurophysiol. 1999; 81:1104–12. [PubMed: 10085337]
10. Nackley AG, Tan KS, Fecho K, Flood P, Diatchenko L, Maixner W. Catechol-O-methyltransferase inhibition increases pain sensitivity through activation of both beta(2)- and beta(3)-adrenergic receptors. Pain. 2006

11. Baerwald CG, Laufenberg M, Specht T, von Wichert P, Burmester GR, Krause A. Impaired sympathetic influence on the immune response in patients with rheumatoid arthritis due to lymphocyte subset-specific modulation of beta 2-adrenergic receptors. Br J Rheumatol. 1997; 36:1262–9. [PubMed: 9448586]
12. Kaplan R, Robinson CA, Scavulli JF, Vaughan JH. Propranolol and the treatment of rheumatoid arthritis. Arthritis Rheum. 1980; 23:253–5. [PubMed: 7362673]
13. Levine JD, Fye K, Heller P, Basbaum AI, Whiting-O'Keefe Q. Clinical response to regional intravenous guanethidine in patients with rheumatoid arthritis. J Rheumatol. 1986; 13:1040–3. [PubMed: 3550071]
14. Mannisto PT, Kaakkola S. Catechol-O-methyltransferase (COMT): biochemistry, molecular biology, pharmacology, and clinical efficacy of the new selective COMT inhibitors. Pharmacol Rev. 1999; 51:593–628. [PubMed: 10581325]
15. Diatchenko L, Slade GD, Nackley AG, et al. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. Human Molecular Genetics. 2005; 14:135–43. [PubMed: 15537663]
16. McLean SA, Diatchenko L, Lee YM, et al. Catechol O-Methyltransferase Haplotype Predicts Immediate Musculoskeletal Neck Pain and Psychological Symptoms After Motor Vehicle Collision. The Journal of Pain. 2011; 12:101–7. [PubMed: 20688576]
17. Bijur PE, Latimer CT, Gallagher EJ. Validation of a verbally administered numerical rating scale of acute pain for use in the emergency department. Acad Emerg Med. 2003; 10:390–2. [PubMed: 12670856]
18. [Accessed July, 2011] Interagency guidline on opioid dosing for chronic non-cancer pain: an educational aid to improve care and safety with opioid therapy. 2010. at http://www.agencymeddirectors.wa.gov/Files/OpioidGdline.pdf
19. Ashton, H. Benzodiazepine Equivalency Table. 2007. http://wwwbcncorguk/equivalencehtml
20. Nackley AG, Shabalina SA, Tchivileva IE, et al. Human Catechol-O-Methyltransferase Haplotypes Modulate Protein Expression by Altering mRNA Secondary Structure. Science. 2006; 314:1930–3. [PubMed: 17185601]
21. Diatchenko L, Nackley AG, Slade GD, et al. Responses to Drs. Kim and Dionne regarding comments on Diatchenko, et al. Catechol-O-methyltransferase gene polymorphisms are associated with multiple pain-evoking stimuli. Pain. 2007; 129:366–70. [PubMed: 17851590]
22. Nackley AG, Shabalina SA, Lambert JE, et al. Low Enzymatic Activity Haplotypes of the Human Catechol-O-Methyltransferase Gene: Enrichment for Marker SNPs. PLoS ONE. 2009; 4:e5237. [PubMed: 19365560]
23. Shibata K, Diatchenko L, Zaykin DV. Haplotype associations with quantitative traits in the presence of complex multilocus and heterogeneous effects. Genetic Epidemiology. 2009; 33:63–78. [PubMed: 18636529]
24. Browne AL, Andrews R, Schug SA, Wood F. Persistent Pain Outcomes and Patient Satisfaction With Pain Management After Burn Injury. The Clinical Journal of Pain. 2011; 27:136–45.10.1097/AJP.0b013e3181f7f9bb [PubMed: 21268301]
25. [Accessed April, 2011] National Burn Repository 2011 Report. 2011. at http://www.ameriburn.org/2011NBRAnnualReport.pdf

Table 1

Participant Characteristics

	n (%)
n	57
Age (mean±SD)	32±10
Male (n,%)	45 (79)
Ethnicity (n,%)	
European American	39 (68)
African American	15 (26)
Other	3 (5)
Total body surface area (TBSA) of burn (n,%)	
1-5%	21 (37)
6-10%	20 (35)
11-15%	11 (19)
16-20%	5 (9)
Total body surface area (TBSA) of burn that was 3rd Degree (n,%)	
0%	34 (60)
1-5%	18 (32)
6-10%	5 (9)
Type of thermal burn (n,%)	
Flame	26 (46)
Grease	13 (23)
Scald	14 (25)
Contact	4 (7)
COMT pain vulnerable genotype * (n,%)	
Yes	25 (44)
No	32 (56)

* Defined as *COMT* genotype which does not contain 1 or more “low pain sensitivity” haplotypes.

Table 2

Association of *COMT* Genotype with Pain Scores Post-Burn

	COMT Pain Vulnerable Genotype*				
	Yes		No		
	Mean	SE	Mean	SE	p-value
Unadjusted					
Least	4.1	0.3	2.8	0.3	.006
Waking	7.1	0.3	5.6	0.3	.001
Worst	8.8	0.3	8.7	0.3	.790
Overall†	6.7	0.3	5.7	0.2	.011
Adjusted‡					
Least	3.8	0.5	2.6	0.4	.017
Waking	6.8	0.5	5.3	0.4	.004
Worst	8.5	0.5	8.4	0.4	.898
Overall†	6.3	0.4	5.4	0.4	.037

*Defined as *COMT* genotype which does not contain 1 or more “low pain sensitivity” haplotypes.

†Linear mixed modeling was used to combine six pain measurements (waking, worst, and least pain assessed each day for two consecutive days) for each individual into an overall pain score. See Methods for details.

‡Adjusted for TBSA, burn depth, age, gender, ethnicity, and time from admission to assessment.

Table 3
Association Between Selected Patient Characteristics and Overall Pain Score

	Overall Pain Severity*	
	Mean±SE	p-value
Gender		
Male	6.0±.2	.305
Female	6.5±.4	
Age		
≤40 years	6.0±.2	.878
>40 years	6.2±.4	
Ethnicity		
White	6.2±.2	.031
Black	6.3±.4	
Other	4.2±.8	
Time from admission to study assessment†		
≤1 day	6.4±.3	.103
>1 day	5.8±.3	
Thermal burn type		
Flame	6.1±.3	.887
Other	6.1±.3	
Total Body Surface Area burned		
0-5%	6.3±.3	.544
>5%	6.0±.2	
Total Body Surface Area 3rd degree burned		
0%	5.9±.2	.254
>0%	6.4±.3	
COMT pain vulnerable genotype‡		
Yes	6.7±.3	.011
No	5.7±.2	

*Linear mixed modeling was used to combine six pain measurements (waking, worst, and least pain assessed each day for two consecutive days) for each individual into an overall pain score. See Methods for details.

†Time elapse between admission for burn care and the first day of the two-day study period.

‡Defined as *COMT* genotype which does not contain 1 or more “low pain sensitivity” haplotypes.