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Genetic Polymorphisms in the Dopamine Receptor 2 Predict Acute Pain Severity after Motor Vehicle Collision

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Abstract

Objectives: Dopaminergic signaling is implicated in nociceptive pathways. These effects are mediated largely through dopamine receptors and modulated in part by dopamine transporters. This study tests the hypothesis that genetic variants in the genes encoding dopamine receptor 2 (DRD2) and the dopamine active transporter (SLC6A3) influence acute pain severity after motor vehicle collision (MVC).

Methods: European Americans presenting to the emergency department (ED) after MVC were recruited. Overall pain intensity in ED was assessed using a 0-10 numeric rating scale. DNA was extracted from blood samples and genotyping of single nucleotide polymorphisms (SNPs) in the DRD2 and SLC6A3 gene was performed.

Results: A total of 948 patients completed evaluation. After correction for multiple comparisons, SNP rs6276 at DRD2 showed significant association with pain scores, with individuals with the A/A genotype reporting lower mean pain scores (5.3, 95% CI 5.1 to 5.5) than those with A/G (5.9, 95% CI 5.6 to 6.1) or G/G (5.7, 95% CI 5.2 to 6.2) genotypes ($p=0.0027$). Secondary analyses

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revealed an interaction between sex and DRD2 SNPs rs4586205 and rs4648318 on pain scores: females with two minor alleles had increased pain intensity, whereas males with two minor alleles had less pain than individuals with a major allele (interaction $p=0.0019$).

Discussion: Genetic variants in DRD2 are associated with acute pain after a traumatic stressful event. These results suggest that dopaminergic agents may be useful for the treatment of individuals with acute post-traumatic pain as part of a multimodal opioid-sparing analgesic regimen.

Keywords

Dopamine; DRD2; SLC6A3; genetic association; acute trauma

Introduction

Physiologic systems mediating acute pain in humans experiencing stressful/traumatic events remain poorly understood, limiting the development of new treatment options. One physiologic stress system which may contribute to acute pain responses in clinical settings is the dopaminergic system.[1, 2] In animal models, central dopaminergic pathways in the insula, striatum, nucleus accumbens, and periaqueductal gray influence nociceptive processing via activation of the dopamine receptor 2 (DRD2).[3-5] In studies of healthy human volunteers, functional imaging studies demonstrate that variation in DRD2-mediated neurotransmission in central brain regions is associated with acute pain intensity in response to experimental pain stimuli.[6, 7]

This endogenous variation in DRD2-mediated signaling is believed to be due, at least in part, to individual genetic differences that affect DRD2 function. Consistent with this hypothesis, genetic variants in *DRD2* have been associated with vulnerability to chronic pain conditions. [8-10] In addition, in a study of healthy human volunteers, genetic variants in the gene for the dopamine active transporter (*DAT1* or *SLC6A3*), which terminates the effect of dopamine and other monoamines in the synapse, were found to predict the severity of acute experimental pain.[11] Together the above evidence suggests that genetic variants in *DRD2* and *SLC6A3* may influence acute pain severity among individuals experiencing stressful/traumatic events. If this was demonstrated to be the case, then this would provide valuable evidence that dopaminergic systems are involved in acute pain in these settings, and would suggest that DRD2 and SLC6A3 may be important components of this pathway.

One of the most common types of stressful/traumatic events experienced worldwide is motor vehicle collision (MVC), with more than 50 million MVCs occurring each year. [12] Individuals experiencing MVC constitute a relatively homogenous injury population: even among individuals who present to the emergency department for evaluation after MVC, more than 90% have musculoskeletal strain alone [13]. The relatively homogenous nature of the injuries experienced by this population, together with the fact that acute pain in this population is the norm [13], make this a valuable, clinically relevant population in which to evaluate the potential impact of dopaminergic systems on acute pain.

In this study we evaluated the association between genetic variants in *DRD2* and *SLC6A3* and acute pain severity in the hours after motor vehicle collision (MVC) among individuals who were evaluated in the emergency department (ED) after MVC and discharged to home. We hypothesized that genetic variants in *DRD2* and *SLC6A3* would predict acute pain severity in the hours after MVC. In addition, because of evidence that the influence of dopaminergic systems on pain may be sex dependent,[14, 15] secondary analyses were performed in which we evaluated for potential sex differences in genotype effects (sex × gene interactions) on acute post-MVC pain.

Materials and Methods

Study participants

Participants were individuals aged 18 to 65 years who presented to one of eight emergency departments (EDs) for care after MVC between February 2009 to October 2011. Only English-speaking individuals who were alert, oriented, and clinically stable were enrolled. Injury scoring of each patient injury was performed using the Abbreviated Injury Scale (AIS), an anatomically-based scoring system that classifies each injury according to its relative severity on a six point ordinal scale.[16] Patients who had spinal, facial, long bone, and skull fractures as well as prisoners, pregnant patients, patients with intracranial injury or laceration with significant hemorrhage, patients who were admitted to the hospital, and patients presenting to the ED more than 24 hours after MVC were excluded. Only patients who identified themselves as European American were recruited in order to reduce population stratification bias in genetic association analyses.[17] The study was approved by the Institutional Review Board at each study site (Bay State Medical Center, Springfield, MA; Beaumont Hospital, Troy, Michigan, USA; Beaumont Hospital, Royal Oak, Michigan, USA; Massachusetts General Hospital, Boston, Massachusetts, USA; North Shore University Hospital, Manhasset, New York, USA; Saint Joseph Mercy Health System, Ann Arbor, Michigan, USA; Spectrum Health, Grand Rapids, Michigan, USA; Shands Jacksonville, Jacksonville, Florida, USA). All participants gave written informed consent.

Data collection procedures

Potentially eligible patients were approached by a research assistant to determine eligibility. The research assistant informed patients of the voluntary nature of their participation, discussed the risks and benefits of the study, and informed patients that their participation could be withdrawn at any time. In addition, in order to assess patient competency to give informed consent, patients were required to describe the essential elements of the study back to the research assistant. Following consent, study participants completed an ED interview using a web-based survey. Before enrolling patients in the ED, each research assistant completed a study training module followed by an interview with a standardized mock ED patient. Comparison of mock ED patient data across research assistants demonstrated high concordance, with an error rate of 1.3%. To enhance participation and to compensate participants for their time during their ED visit, study participants were provided with \$80.00 remuneration for completing the ED interview.

Measures

Demographic information was collected using standardized questionnaire items. Current overall pain severity was assessed via a numeric rating scale (NRS) ranging from 0 (“no pain”) to 10 (“worst pain possible”). If participants reported pain, they were also asked whether the pain was related to the MVC. Analgesic use in ED was obtained from medical records. Additional details regarding the study design and measurements have been published.[18]

DNA collection and genotyping

Blood (8.5 mL) was collected in the ED using PAXgene™ DNA storage tubes. Blood samples were then refrigerated at the study site and shipped in batches every 2 weeks to Beckman Coulter Genomics, Inc, Morrisville, NC. DNA purification was performed using PAXgene™ blood DNA kit (Qiagen, Valencia, CA). Average DNA yield was 275 µg per sample. Genotyping was performed in batches using the Sequenom platform (Sequenom, Inc., San Diego, CA). SNPs were chosen to cover genotypic diversity of the DRD2 and SLC6A3 genes. Two Hapmap samples and 2 repeat samples were included in each genotyping batch (96 samples) to ensure genotypic accuracy and reliability. Repeated genotyping demonstrated greater than 98% call agreement. The individuals performing genotyping of the DNA samples were blinded to participant pain scores or other clinical data.

Analyses

All genotyped SNPs were tested for Hardy-Weinberg equilibrium (HWE) using a chi-square test with Bonferroni adjustment for multiple testing. Linkage disequilibrium between SNPs was explored by calculating Levontin D' and squared correlation r^2 using HaploView.[19]

The main effects of SNP genotypes on acute pain intensity were evaluated using a general linear model. As the genetic model of association was unknown, a genotypic, dominant, and recessive model were used to evaluate main effects. Study site was included as a covariate in these models, to adjust for potential genetic heterogeneity between study recruitment centers. Patient sex was also included as a covariate in the models. Family-wise Type I error rate was controlled for by applying Bonferroni correction to the significance threshold alpha. The number of effective tests was evaluated by using the method of spectral decomposition. [20] Interactions between patient sex and genotype showing a significant main effect were assessed by introducing the corresponding product term into the model. Post-hoc comparisons were evaluated for statistical significance (alpha = 0.05). Statistical analyses were performed using SAS 9.3 (SAS Institute, Inc., Cary, NC).

Results

A total of 10,629 patients were screened, 1416 were found to be eligible, 969 consented to study participation, and 948 completed evaluation (Fig. 1). Demographic data are provided in Table 1. Consistent with study exclusion criteria, participants had only minor injury: 99% of participants had a maximum AIS score of one, and the remaining participants had an AIS score of two. Minor lacerations were present in 53/948 (6%) participants, and a minor

fracture of a phalanx was present in one individual. Among the 21 SNPs genotyped, one SNP (rs4986918) was monoallelic and was excluded from the analyses. Two SNPs rs6279 and rs27072 had relatively low call rates of 88%. However, as these SNPs have been found in prior studies to have associations with various pathologic phenotypes[21-23], and as other quality metrics (e.g., minor allele frequency and the HWE test) suggested that calls made were correct, these SNPs were included in further analysis. All tested SNPs were in Hardy-Weinberg equilibrium (measured by Pearson χ^2 test, $df = 1$, Bonferroni-adjusted p-value threshold 0.0025) in this study population (Fig. 2).

In analyses evaluating main effects, two SNPs in *DRD2* (rs6279 and rs6276) and one SNP in *SLC6A3* (rs463379) were associated with acute post-MVC pain severity at the nominal significance level of $p < 0.05$ (Table 2). After controlling for multiple comparisons using the method of spectral decomposition (8 effective tests for *SLC6A3* and 8 effective tests for *DRD2*, 16 tests total), only the *DRD2* SNP rs6276 continued to show a statistically significant main effect association with acute pain severity. Mean pain intensity among patients with an A/A genotype at rs6276 (5.3, 95% CI 5.1 to 5.5), $n = 448$) was lower than overall pain intensity among individuals with an A/G (5.9, 95% CI 5.6 to 6.1, $n = 396$) or G/G (5.7, 95% CI 5.2 to 6.2, $n = 99$) genotype. A dominant genetic model of this association provided the best fit to the data ($p = 0.0007$, Fig. 3a).

In analyses evaluating gene \times sex interactions, a statistically significant interaction on acute pain severity was observed for *DRD2* SNPs rs4586205 ($p = 0.0027$) and rs4648318 ($p = 0.0019$) (Table 2). Because these two *DRD2* SNPs are in high linkage disequilibrium (Fig. 2b), only SNP rs4648318 (which showed the more significant interaction) was used in subsequent sex-stratified analyses (Fig. 3c). Among females, those with a G/G or A/G genotype at rs4648318 experienced more severe acute pain than those with an A/A genotype ($p = 0.004$). Among males, those with a G/G genotype experienced less severe acute pain than those with an A/A or A/G genotype ($p = 0.039$). Patient sex also appeared to modify the effect of rs6276 on pain scores (interaction $p = 0.030$, non-significant after Bonferroni adjustment), with the A/G genotype associated with relatively increased pain in males and relatively decreased pain in females (Fig 3b).

Discussion

In this observational study of adult European Americans evaluated in the ED, genetic variants in *DRD2* were associated with acute pain severity in the hours after MVC. *DRD2* SNP rs6276 showed a statistically significant main effect association with acute post-MVC pain severity. The evaluation of gene \times sex interactions, performed because of substantial evidence that the influence of dopaminergic systems on pain may be sex dependent,[14, 15] suggests that the effect of rs6276 genotype on acute pain may indeed be sex specific. In addition, *DRD2* SNPs rs4648318 and rs4586205 also predicted acute post-MVC pain severity in a sex-specific manner.

The function of these significant *DRD2* SNPs is difficult to elucidate as they are in non-coding regions of the gene, though there is some literature on their phenotypic effects. SNP rs6276 is located in the 3'-untranslated region (UTR) of the *DRD2*, a region known to be

important in the stability of mRNA and mRNA regulation. Using SNPfunc and regulomeDB, rs6276 does have putative microRNA binding sites and may also be involved in the binding of transcription factor Ikaros family zinc finger protein 1 (IKZF1) and CCCTC-Binding factor (CTCF).[24, 25] At this location, it is not expected to alter the protein structure of the dopamine receptor. However, rs6276 has been associated with various behavioral and psychiatric disorders.[26-31] Functionally, there is a described effect of this polymorphism: compared to those with the A/G or G/G genotype, individuals with the A/A genotype at rs6276 have been shown to have reduced release of growth hormone in response to apomorphine (a surrogate measure of central dopamine receptor function).[32, 33] In addition, the rs6276 G allele is in linkage disequilibrium (HapMap database release 27) with at least two non-synonymous polymorphisms which may also affect clinical outcomes: a) rs1801028 (Ser311Cys), known to be associated with reduced DRD2 activity, and b) rs1800497 (also known as the TaqIA A1), located in the coding region of the neighboring ANKK1 gene, whose T allele is associated with increased dopamine synthesis from L-dopa. [34, 35] Of note, a T allele at rs1800497 has also been shown to correlate with low dopaminergic signaling.[36] The rs6276 G allele is also in high linkage disequilibrium ($r^2=0.95$) with the rs6275 T allele (NcoI or C939T) which is associated with increased risk of schizophrenia, increase in prolactin in olanzapine-treated women, and response to treatment regimens for migraines.[22, 37-39] SNPs rs4648318 and rs4586205 are located in an intronic sequence in *DRD2*; variations in these non-coding regions are known to regulate expression of protein splice variants or affect protein levels.[40] Although rs4648318 has been weakly associated with nicotine dependence and Tourette syndrome[23, 41] little is known of the functional effect of this SNP.

In summary, the A/A genotype of rs6276 is known to lead to reduced dopaminergic signaling,[32, 33] and in our population individuals with the A/A genotype had significantly lower pain scores. This potentially supports a simple linear model where greater dopaminergic signaling through DRD2 leads to greater acute pain scores. However, evaluation of sex-specific effects suggests that the relationship between dopaminergic signaling through DRD2 and pain is more complex.

As noted above, differences in dopaminergic signaling between sexes have long been appreciated.[42, 43] Females have been found to have higher basal central dopaminergic signaling in both human and animal studies.[44] Taken together, our gender results best fit the “inverted-U” model of dopaminergic signaling,[1, 45, 46] whereby both a relative deficiency and a relative excess of dopamine receptor signaling results in increased pain. This model fits well with our results, and may explain why in males, with generally lower levels of DRD2 signaling,[44] the G/G genotype (which is associated with greater dopaminergic signaling[32]) leads to lower pain scores, while in females, with generally higher levels of DRD2 signaling,[44] the A/A genotype (which is associated with less dopaminergic signaling[32]) leads to lower pain scores.

This “inverted-U” model may also explain why pain treatments for individuals with abnormal dopamine processing vary according to whether a dopamine deficiency or excess is present. In patients with a paucity of dopamine, such as those with Parkinson’s disease, lower pain tolerances are correlated with the absence of dopamine and ameliorated by its

replacement.[47, 48] In diseases such as migraine headaches, in which there are elevated dopamine levels during acute migraine attacks,[49] dopaminergic antagonists such as metoclopramide and olanzapine appear to be analgesic.[50]

We hypothesized that polymorphisms in *SLC6A3* would also be associated with nociception. SNP rs463379 was associated with pain scores before adjustment for multiple comparisons, but after adjustment was only associated with statistical significance at the trend level. As noted previously, although one group found an association between *SLC6A3* variants and experimental pain in healthy human volunteers, in a subsequent study they were unable to find an association between this transporter and endogenous pain modulation.[11, 51] Another study could not find an association between *SLC6A3* SNPs (including rs403636) and acute postoperative pain among individuals undergoing third molar extraction.[52] Our study provides only a weak evidence for an association between *SLC6A3* variants and acute clinical pain after MVC trauma.

Several limitations should be considered when interpreting our results. First, the magnitude of the differences in pain score according to genotype identified in this study were small. However, we have found that the risk G allele at rs6276 was positively associated with both opioid analgesic use in ED (Chi-square test $p=0.03$) and pain severity in ED, suggesting that the association of the SNP with pain may be attenuated by analgesic use. Importantly, the magnitude of influence of an individual SNP on a biologic pathway is not necessarily proportional to the influence of the overall pathway or indicative of whether the pathway is an important/druggable target. For example, individual common genetic variants in LDL cholesterol or μ -adrenergic pathways can have only small effects on endophenotypes or clinical outcomes,[53, 54] however medications targeting these pathways have advanced the care of patients with coronary artery disease.[55] In this regard, it should be noted that the purpose of this analysis was to assess whether dopaminergic signaling has an influence on acute pain outcomes, by assessing only a few of the many potential genetic variants influencing only two of the components of dopaminergic neurotransmission pathways.

Another limitation of the study is that, as discussed above, we do not know if the SNPs associated with acute pain severity in this study are themselves functional or are in linkage disequilibrium with the actual functional allele(s). Further studies are needed to identify the precise DRD2 functional alleles associated with acute pain severity, and to evaluate the molecular changes mediated by the identified genetic variants. Future studies may be strengthened by examining the mRNA profile to corroborate SNPs in the genomic DNA with an mRNA profile from the peripheral blood cells. Ideally, dopamine levels centrally would be assessed. In addition, the involvement of dopaminergic signaling in cognitive and psychological responses which are interwoven with the neurosensory processing of acute pain makes it challenging to isolate the direct effect of dopaminergic genetic variants on neurosensory processing vs. the indirect effects of these variants mediated by cognitive and psychological factors. Therefore both direct and indirect effects of dopaminergic genetic variants were assessed in the present study. Lastly, while the cohort size of this candidate gene association study was relatively large, the lack of an available replication cohort increases the possibility of a false positive result (type I error). Our findings lack an independent cohort for verification and require replication in other cohorts of patients with

acute pain after MVC and in cohorts of patients with acute pain after other forms of stress exposure/tissue injury such as acute postoperative pain. However, we believe that from a Bayesian viewpoint, our evaluation of focused hypotheses within a biologic pathway with proven preclinical and clinical evidence of involvement in nociceptive processing reduces this risk.

In conclusion, our study findings support the hypothesis that dopaminergic signaling through *DRD2* is involved in nociceptive processing.[5, 56] While dopamine antagonists are used for management of acute migraine attacks by emergency medicine physicians,[50] few studies of dopaminergic agents for non-headache conditions have been performed.[57-61] Our results suggest that variation in dopaminergic signaling is associated with acute pain severity after MVC. If confirmed by future validation cohorts, these results suggest that dopaminergic agents may be useful for pain control in other clinical conditions and settings, such as individuals with acute post-traumatic pain and acute postoperative pain, as part of a multimodal opioid-sparing analgesic regimen.

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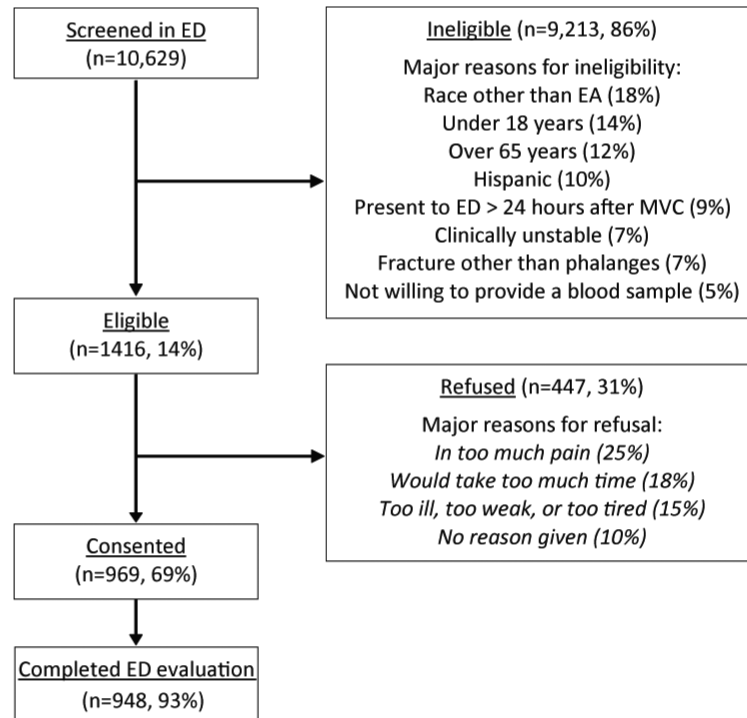


Figure 1. Study flowchart. ED = Emergency Department. EA = European American. MVC = Motor Vehicle Collision.

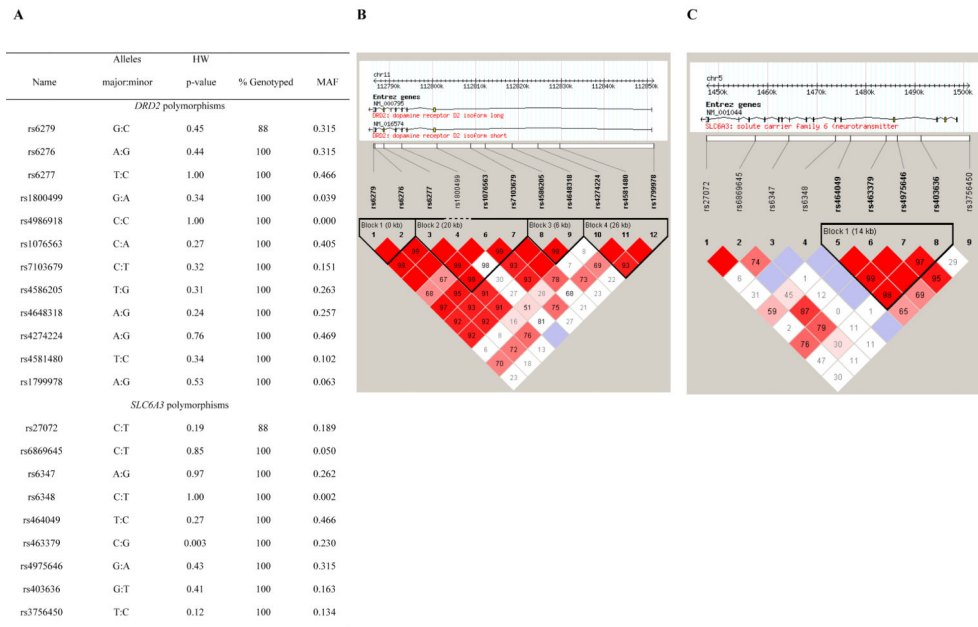


Figure 2. The table in Panel A delineates the SNPs examined in this study, arranged in genomic order and grouped by gene. The Hardy-Weinberg equilibrium p-value was computed using Haploview. MAF describes the minor allele frequency as noted in this cohort. Panels B and C show the linkage disequilibrium of *DRD2* and *SLC6A3* SNPs, respectively. As noted in the text, SNP rs4986918 was monoallelic in this population.

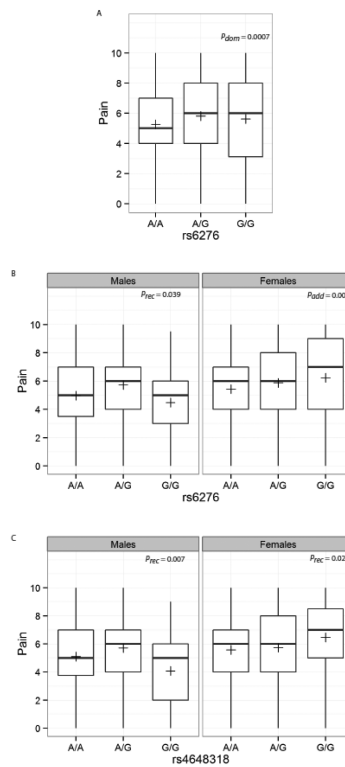


Figure 3.

Acute pain scores by DRD2 genotypes A) Among all participants for rs6276; B) Among males or females for rs6276 (rs6276×sex interaction $p = 0.030$, non-significant after correction for multiple testing); C) Among males or females for rs4648318 (rs4648318 ×sex interaction $p = 0.0019$). Box plots represent median, lower and upper quartile, and range. Means are represented by a (+) symbol. Only those p-values which provided best fit to the data (lowest p-values) are shown; rec = recessive; dom = dominant; add = additive.

Table 1

Study participant characteristics.

Variable		N = 948	
Age (Mean \pm SD), years		36 \pm 13	
Range, years		18-65	
		<i>n</i>	%
Females		575	61.0
	8-11 years	42	4.4
	12 years or completed high school	184	19.4
	Post high school training other than college	57	6.0
Education	Some college	312	32.9
	College graduate	238	25.1
	Post graduate level	113	11.9
	No data	2	0.2
	\$0-\$19,999	117	12.3
	\$20,000-\$39,999	176	18.6
	\$40,000-\$59,999	161	17.0
	\$60,000-\$79,999	116	12.2
Income			
	\$80,000-\$99,999	91	9.6
	\$100,000-149,999	98	10.3
	\$150,000 or higher	84	8.9
	No data / Refused	105	11.1
Acute Pain in ED	None or mild (0-3 NRS)	188	20.0
	Moderate (4-6 NRS)	407	43.3
	Severe (7-10 NRS)	344	36.6

NRS = Numerical Rating Scale

Table 2

Associations between DRD2 and SLC6A3 genotypes, acute pain intensity, and sex.

SNP	Alleles (M:m)		Genotype M/M	Genotype M/m	Genotype m/m	Main effect p-value	Gene × sex p-value
Dopamine Receptor 2 gene (<i>DRD2</i>)							
rs6279	G:C	Mean	5.3	5.8	5.7	0.032	0.021
		95% CI	5.1, 5.6	5.5, 6.0	5.2, 6.2		
rs6276	A:G	Mean	5.3	5.9	5.7	0.0027*	0.030
		95% CI	5.1, 5.5	5.6, 6.1	5.2, 6.2		
rs6277	T:C	Mean	5.5	5.6	5.6	0.64	0.64
		95% CI	5.2, 5.7	5.4, 5.8	5.3, 6.0		
rs1800499	G:A	Mean	5.6	5.2	7.7	0.14	0.65
		95% CI	5.4, 5.8	4.6, 5.8	5.0, 10.4		
rs1076563	C:C	Mean	5.5	5.6	5.6	0.79	0.62
		95% CI	5.2, 5.8	5.4, 5.9	5.2, 6.0		
rs7103679	C:A	Mean	5.7	5.3	5.2	0.19	0.10
		95% CI	5.5, 5.8	5.0, 5.7	4.3, 6.1		
rs4586205	C:T	Mean	5.4	5.8	5.8	0.081	0.0027*
		95% CI	5.2, 5.6	5.5, 6	5.2, 6.3		
rs4648318	T:G	Mean	5.4	5.8	5.6	0.13	0.0019*
		95% CI	5.2, 5.6	5.5, 6.0	5.1, 6.2		
rs4274224	A:G	Mean	5.5	5.6	5.6	0.96	0.61
		95% CI	5.2, 5.8	5.4, 5.8	5.2, 5.9		
rs4581480	A:G	Mean	5.5	5.8	5.7	0.37	0.76
		95% CI	5.3, 5.7	5.4, 6.2	4.4, 7.0		
rs1799978	T:C	Mean	5.6	5.6	8.2	0.31	0.55
		95% CI	5.4, 5.7	5.1, 6.0	4.8, 11.5		
Dopamine Transporter gene (<i>SLC6A3</i>)							
rs27072	C:T	Mean	5.6	5.4	5.9	0.33	0.96
		95% CI	5.4, 5.8	5.1, 5.7	5.1, 6.7		
rs6869645	C:T	Mean	5.6	5.7	5.9	0.83	0.012
		95% CI	5.4, 5.7	5.2, 6.2	3.2, 8.7		
rs6347	A:G	Mean	5.6	5.5	5.5	0.85	0.54
		95% CI	5.4, 5.8	5.3, 5.8	4.9, 6.1		
rs6348	C:T	Mean	5.6	7.2	-	0.24	NE
		95% CI	5.4, 5.7	4.5, 9.9	-		
rs464049	T:C	Mean	5.3	5.7	5.7	0.11	0.27
		95% CI	5.0, 5.6	5.4, 5.9	5.3, 6.0		
rs463379	C:G	Mean	5.4	5.8	6.0	0.047	0.47
		95% CI	5.2, 5.6	5.5, 6.0	5.4, 6.6		
rs4975646	G:A	Mean	5.7	5.4	5.6	0.39	0.85
		95% CI	5.4, 5.9	5.2, 5.7	5.1, 6.1		

SNP	Alleles (M:m)		Genotype M/M	Genotype M/m	Genotype m/m	Main effect p-value	Gene × sex p-value
rs403636	G:T	Mean	5.6	5.5	4.4	0.093	0.87
		95% CI	5.4, 5.8	5.2, 5.8	3.4, 5.5		
rs3756450	T:C	Mean	5.6	5.6	5.8	0.88	0.97
		95% CI	5.4, 5.7	5.2, 5.9	4.8, 6.8		

For genotypes, 'M' refers to the reference (major) allele whereas 'm' refers to the minor allele. The overall pain intensity by genotype is shown as mean and 95% confidence interval (CI). P-values are adjusted for study site and sex. NE=non-estimable.

* denotes a p-value which is significant after controlling for multiple comparisons.

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