Observational Study

Resistin Gene Polymorphism is an Influencing Factor of Postoperative Pain for Chinese Patients

Han Xie, MD[1], Qingqing Fan, MD[1], Zhengliang Ma, PhD[2], Zhengxiang Chen, MD[3], Qing Shu, PhD[1], Danying Li, PhD[1], and Weihong Ge, MD[1]

From: [1]Department of Pharmacy, [2]Department of Anesthesiology, [3]Department of Spine Surgery, The Affiliate Drum Tower Hospital of Nanjing University Medical School, 210008, Nanjing

Address Correspondence: Weihong Ge, MD Department of Pharmacy, The Affiliate Drum Tower Hospital of Nanjing University Medical School No.321 Zhongshan Rd Nanjing City, Jiangsu Province, 210008, PR China E-mail 6221230@sina.com.

Disclaimer: Jiangsu Medical Innovation Team (Leading Talents) Project. Project Number: CXTDA2017041

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 11-17-2019 Revised manuscript received: 02-02-2020 Accepted for publication: 03-03-2020

Free full manuscript: www.painphysicianjournal.com

Background: Gene polymorphism is an important factor affecting the efficacy and dosage of opioids. A recent study showed RETN rs3745367 was associated with postoperative pain intensity. OPRM1 gene was confirmed to affect the postoperative analgesic consumption of morphine and other opioids.

Objective: In this study, we investigated the association between single nucleotide polymorphisms (SNPs) in the RETN, OPRM1 gene and postoperative pain intensity, analgesics consumption, and ADR. The haplotype analysis focus on OPRM1 was also implemented.

Study Design: This was a prospective, observational study.

Setting: Patients undergoing spinal fusion and correction operation were recruited. Genotypes of rs3745367, rs1799971, rs2075572, and rs9322447 were tested. Pain assessment was performed to measure postoperative pain intensity, postoperative fentanyl and pethidine consumption was recorded to calculate analgesics consumption, and adverse reactions were recorded.

Method: We recruited 142 patients undergoing spinal correction and fusion. Genotyping was performed by using a real-time polymerase chain reactions (PCRs) system and validated with allelic discrimination assays. The pain was assessed using a numerical rating scale (NRS). Statistical analyses were performed using SPSS software. LD test and the construction and analysis of haplotype were using Haploview software.

Results: Rs3745367 demonstrated a significant association with postoperative average pain intensity in 24h ($P = 0.015$) and 48h ($P = 0.001$) after surgery. Rs2075572 and rs9322447 influenced postoperative maximal pain intensity in 48h after surgery (P = 0.042, 0.033, respectively). No correlation was found between OPRM1 SNPs and analgesics consumption and adverse reaction. According to the results of this study, a strong LD was observed between rs1799971 and rs9322447 (Block 1, LD parameters: D′ = 0.82, r^2 = 0.14), rs2075572 and rs9322447 (Block 2, LD parameters: D′ = 0.92, r^2 = 0.51).

Limitations: The association between rs3745367 with serum resistin levels was not investigated in this research, serum resistin levels of the incision part should be investigated in future studies.

Conclusion: RETN rs3745367 was associated with postoperative average pain intensity, OPRM1 rs2075572 and rs9322447 may influence postoperative maximal pain intensity.

Key words: Postoperative pain, RETN, OPRM1, gene polymorphism, haplotype, opioid, morphine

Pain Physician 2020: 23:E695-E702

Opioids are the first choice for the treatment of acute postoperative pain, but the analgesic effect of opioids showed significant individual differences, thus affecting the analgesic effect. The analgesic effect is affected by many factors and the gene polymorphism is the main factor. Postoperative pain is influenced by genetic variant factors such as the nociceptive pain pathway

and the pharmacokinetics and pharmacodynamics of analgesics (1,2).

As we all know, the inflammatory pathway is the primary pathophysiological mechanism of postoperative pain. Inflammatory factors in the incision directly stimulate and maintain inflammatory pain. Previous studies have confirmed a close relationship between postoperative pain and proinflammatory cytokines (3,4).

In recent years, many studies have elucidated the relationship between adipokines and joint pain (5). Basic research confirms that leptin, a kind of adipokines, mediates analgesia enhanced opioid reward in rats (6). Resistin is an adipokine that is related to obesity and associated diseases such as diabetes mellitus. Studies have elucidated the relationship between resistin and rheumatoid arthritis pain (7), osteoarthritis pain (8), and migraine (9,10).

Concerning the relationship between adipokines and inflammation, recent studies point out that adipokines are associated with an increase in proinflammatory cytokines. Furthermore, single nucleotide polymorphisms (SNPs) of adipokines are associated with their serum levels (11). One study showed that a genetic variant of resistin and serum resistin levels were associated with postoperative pain intensity in Japanese individuals (12). Therefore, we hypothesize that the genetic variants of resistin affect postoperative pain and lead to individual variations of pain intensity in Chinese individuals.

The μ-opioid receptor is a primary target for opioid analgesics, including fentanyl. OPRM1 118A>G is one of the most widely studied SNPs. The MAF of OPRM1 118A>G is 36.9% in Chinese people (13), the frequency of OPRM1 118A>G varies with race. Recent studies confirmed the finding that OPRM1 118A>G (rs1799971) alternate individual response to opioid, leading to the change of fentanyl consumption (14); people with G allele consume more fentanyl. But most of the research shows that it did not affect the pain intensity (visual analog scale [VAS] score). OPRM1 IVS2+G 691C (rs2075572) CC is considered relevant to the shorter cold pain tolerance time than those without the CC genotype in Southeast Asia (15). This SNP has a high mutation frequency for Chinese people, and research reported that this SNP is associated with intraoperative remifentanil consumption in Chinese patients. Patients with homozygous for the minor allele (G allele) are statistically significantly higher than patients with heterozygous for the G allele or patients without the G allele (16). The result is still controversial, so further investigation is needed. OPRM1 rs9322447, the minor allele frequency (MAF) of this SNP is 21.4% in Chinese people and there is a significant difference in mutation frequency between Chinese and other nationalities. The influence of this SNP is unclear.

On this basis, we selected one SNP in the RETN gene and 3 in the OPRM1 gene and investigated the associations between these SNPs and postoperative pain intensity, opioids consumption, and side effects. Then we established the haplotype of OPRM1, the frequency of the haplotype was compared between the adverse reactions (ADR) group and normal group in the second part.

Methods

Patients

This subject was approved by the Ethics Committee of Drum Tower Hospital (AF/SC-08/02.0). Eligible patients were recruited from May 2018 to August 2018. Patients with the following criteria were included: (1) diagnosis of idiopathic scoliosis and accepted spinal correction and fusion operation; (2) the patient can cooperate with pain assessment after surgery. Patients were excluded with these conditions: (1) patients with prior surgery; (2) patients with analgesic drug abuse; and (3) lost data. All patients are Han Chinese.

Sample Collection and Genotyping

A sample of 1.5 mL of anti-coagulated venous blood was collected from each patient after surgery. DNA was extracted using the Ezup Column Blood Genome DNA Extraction Kit (B518253, Sangon Biotech, Shanghai). Genotypes were assessed for RETN rs3745367, and OPRM1 rs1799971, rs2075572, and rs9322447 by using a real-time Polymerase chain reactions (PCRs) system (Applied Biosystems, USA) and validated allelic discrimination assays (B600090, Sangon Biotech, Shanghai).

Briefly, 1 ng of genomic DNA was mixed with each assay and PCR universal master mix (Sangon Biotech, Shanghai) in a total volume of 20 μl. Thermal cycler parameters included 25 cycles of denaturation at 96°C for 10 seconds, annealing at 50°C for 5 seconds and extension at 60°C for 4 minutes.

Analgesia and Pain Assessment

All patients accepted the total intravenous anesthesia and posterior spinal correction and fusion operation. Postoperative analgesic plan: patient-controlled

intravenous analgesia (PCIA) was provided 5 minutes before incision closure. PCIA is composed of continuous fentanyl (adult: 15~20 mg/kg, children: 0.3~0.8 mg/kg) and dexamethasone 10 mg and ondansetron 8 mg diluted to a total volume of 100 mL. PCIA was programmed with a background speed of 2mL/h, a bolus dose of 0.5 mL and a 15-minute lockout for breakthrough pain. PCIA bolus times were recorded to calculate analgesics consumption. Intravenous flurbiprofen axetil 50 mg twice per day was administered as a combined analgesic to relieve inflammation. If the analgesia was ineffective, intravenous pethidine 25 mg was used as a rescue analgesic as the patient demanded.

Pain measurement was assessed at multiple time points after surgery by the same postoperative pain management team. Pain intensity was measured by the numerical rating scale (NRS) at 0, 2, 6, 12, 24, 30, 36, and 48 hours after surgery. Intensity scores ranged from 0 to 10 (0: no pain, 10: the most pain).

Data Collection

The patients' gender, age, American Society of Anesthesiologists (ASA) classification, and body mass index (BMI) were recorded. The postoperative average pain in 24 hours and 48 hours after surgery and the postoperative maximal pain after surgery were investigated. Bolus time of PCIA and pethidine rescue times within 24 hours were recorded to calculate oral morphine equivalents (OME) (refer to the OME algorithm) (17). Times of vomiting, nausea, and dizziness after surgery were recorded during the follow-up period.

Data Analysis

Statistical analysis was performed using SPSS Statistics 22.0 software. Continuous variables were presented as the mean ± SD or median (lower quartile, upper quartile) according to its distribution characteristics. Categorical variables were expressed as percentages. Deviations from the Hardy-Weinberg equilibrium (HWE) were tested using the chi-square analysis, $P < 0.05$ was assumed to indicate a deviation from HWE. The Kruskal-Wallis test was used to determine associations between the gene type and pain intensity, OME, and ADR. HaploView 4.2 software was used for the linkage disequilibrium (LD) test and the construction and analysis of the haplotype. To investigate the difference of haplotype frequency groupings by ADR, the difference of haplotype frequency between the ADR group and the normal group was compared by the Chi-square test. The difference was considered to be statistically significant when $P < 0.05$.

Results

Patients Characteristics and Genotype Distribution

A total of 142 patients were included in this study. The demographic characteristics of the patients are described in Table 1.

The genotype distributions of the RETN gene SNP (rs3745367) and the 4 OPRM1 gene SNPs (rs1799971, rs2075572, rs9322447) are shown in Table 2. All the genotype distributions conformed with the HWE and previous reports in Chinese Han populations.

Table 1. *Demographic characteristics*.

Characteristics	
Age (years)	16 ± 5
Sex (female,%)	96 (67.6%)
BMI (kg/m^2)	14.9 ± 2.5
ASA (II,%)	85 (59.9%)
Duration of operation (min)	265 ± 75
Pain intensity (NRS) 24h average 48h average Maximal	 2.16 ± 1.52 2.05 ± 1.40 4.01 ± 2.50
OME total (mg)	145.91 ± 69.85
Adverse reaction (n,%) Vomiting Nausea Dizziness	 33 (23.2%) 35 (24.6) 14 (9.9%)

Table 2. *Genotype distribution of RETN and OPRM1*.

SNPs	MAF	Major homozygotes	Heterozygotes	Minor homozygotes	HWE
rs3745367	35.9%	GG (54, 38.0%)	AG (74, 52.1%)	AA (14, 9.9%)	0.290
rs1799971	40.1%	AA (52, 36.6%)	AG (66, 45.5%)	GG (24, 16.9%)	0.926
rs2075572	34.5%	CC (63, 44.4%)	CG (60, 42.3%)	GG (19, 13.4%)	0.740
rs9322447	23.9%	GG (80, 56.3%)	AG (56, 39.4%)	AA (6, 4.2%)	0.615

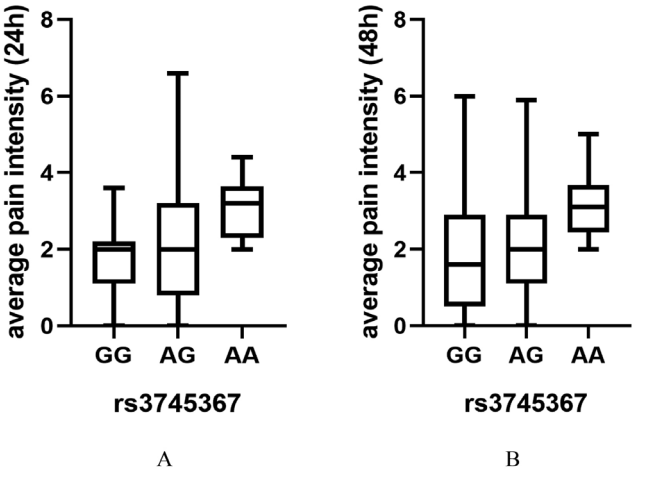

Fig. 1. *A. Postoperative average pain intensity of different genotypes of rs3745367 in 24 hours after surgery. B. Postoperative average pain intensity of different genotypes of rs3745367 in 48 hours after surgery.*

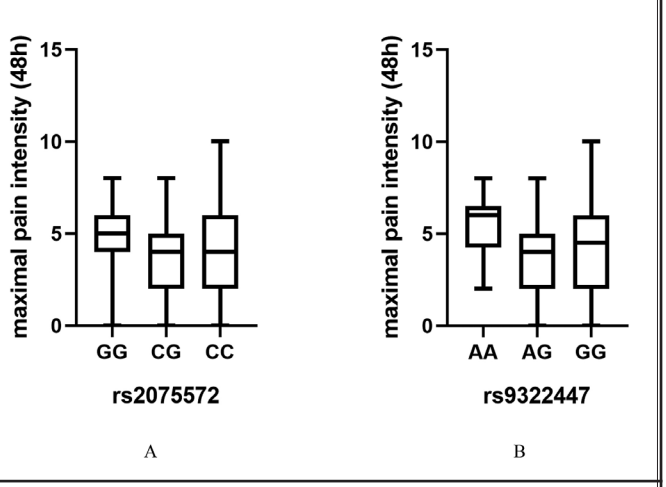

Fig. 2. *A. Postoperative maximal pain intensity of different genotypes of rs2075572 in 48 hours after surgery. B. Postoperative maximal pain intensity of different genotypes of rs 9322447 in 48 hours after surgery.*

The Influence of the RETN Polymorphism on Pain Intensity

According to the results, rs3745367 demonstrated a significant association with postoperative average pain intensity in 24 hours (P = 0.015) and 48 hours (P = 0.001) after surgery. Compared to patients with GG (24 hour NRS = 1.94 ± 1.53, 48 hour NRS = 1.72 ±1.35) and AG (24 hour NRS = 2.15 ± 1.55, 48 hour NRS = 2.07 ± 1.42) genotypes, patients with AA (24 hour NRS = 3.10 ± 0.85, 48 hour NRS = 3.20 ± 0.87) genotype complained about severe pain. Also, rs3745367 is irrelevant with the maximal pain intensity in 48 hours after surgery (Figs. 1A, 1B).

The Influence of the OPRM1 Polymorphisms on Pain Intensity, Opioids Consumption and Adverse Reactions

According to our results, rs2075572 and rs9322447 influences postoperative maximal pain intensity in 48 hours after surgery (P = 0.042, 0.033, respectively), but not postoperative average pain intensity in 24 hours and 48 hours after surgery (Figs. 2A, 2B). Compared with CC type (4.17 ± 2.76) and CG type (3.52 ± 2.22), patients with the GG type (NRS = 5.05 ± 2.15) of rs2075572 complained about more serious pain. For rs9322447, patients with AA type (NRS = 5.50±1.98) complained about more serious pain than GG type (NRS = 4.33 ± 2.67) and AG type (NRS = 3.41 ± 2.18). Rs1799971 is irrelevant to pain intensity.

Opioid consumption was investigated in this study. The dose of fentanyl and pethidine were converted into OME to measure opioid consumption. The results showed that no SNPs in the OPRM1 gene expressed a significant association with OME in 48 hours after surgery (Table 3).

The distribution of different genotypes of OPRM1 SNPs among groups was compared according to the occurrence of ADR. No SNPs in the OPRM1 gene showed a significant association with vomiting, nausea, and dizziness (Table 4).

Linkage Disequilibrium Test and Haplotype Analysis

According to the results of the study, a strong LD was observed between rs1799971 and rs9322447 (Block 1, LD parameters: D′ = 0.82, r^2 = 0.14), and rs2075572 and rs9322447 (Block 2, LD parameters: D′ = 0.92, r^2 = 0.51) (Figs. 3A, 3B).

Four haplotypes were found in block 1: rs1799971G/rs9322447G (38.5%), rs1799971A/rs9322447G (37.6%), rs1799971A/rs9322447A

(22.3%), and rs1799971G/rs9322447A (1.7%). Four haplotypes were found in block 2: rs2075572C/rs9322447G (64.2%), rs2075572G/rs9322447A (22.7%), rs2075572G/rs9322447G (11.8%), and rs2075572C/rs9322447A (1.3%).

At the end of this part, we investigated the difference of haplotype frequencies grouping by ADR, and the difference of haplotype frequency between ADR group and normal group. The result showed that the haplotype blocks we constructed were not associated with ADR (Table 5).

Discussion

Numerous pharmacogenetic studies have focused on the effect of gene polymorphisms on the consumption, efficacy, and side effects of opioids in recent years. This study shows the first investigation of the association between RETN rs3745367 and the postoperative pain intensity in Chinese adolescent scoliosis patients. We explored the association between postoperative opioids consumption, pain intensity and ADR with OPRM1 rs1799971, rs2075572, and rs9322447.

Resistin, as a proinflammatory cytokine, is expressed and secreted by monocytes and macrophages, and plays an important role in the pathophysiology of inflammatory conditions. Previous studies proved that resistin is associated with osteoarthritis pain (18,19), and RETN gene polymorphism is associated with serum resistin levels (20,21). Thus, in addition to these nonspecific inflammatory cytokines such as interleukin-1β, interleukin-6, and TNF-α, resistin and other cytokines may mediate the occurrence of systemic inflammatory conditions after surgery.

In this study, we found that rs3745367 was associated with significant individual differences in the mean NRS score in the 24 hours (P = 0.015) and 48 hours (P = 0.001) after surgery. Compared to patients with GG and AG genotypes, patients with the AA genotype complained about severe pain. Therefore we determined rs3745367 as an impact factor of postoperative pain intensity. This result is the same as the previous study progressed by Hozumi et al (12). But the genotype distribution of rs3745367 is different from the above research, which may due to the sample size. Besides, rs3745367 is irrelevant with the maximal pain intensity in 48 hours after surgery. The above research also investigated the association between pain intensity and the serum of resistin, and the serum resistin level showed a positive association with postoperative pain. Based on the above research results, it is recommended that future research focus on the relationships among the level of resistin in the incision part, pain intensity, RETN gene polymorphism, and so on, but not serum resistin level.

In the second part, we investigated the association between opioids consumption, pain intensity, and ADR with OPRM1 rs1799971, rs2075572, and rs9322447. The results showed that rs2075572 and rs9322447 influence maximal pain intensity in 48 hours after surgery. Patients with the GG type of rs2075572 and patients with the AA type of rs9322447 complained about more serious pain. Liu et al (16) found that the mean intraoperative remifentanil dose necessary to control pain was statistically significantly higher in patients

Table 3. *Summary of the opioid consumption for different genotype groups.*

Genotype		N	OME	*P*
rs1799971	AA	52	1.00 (0.00, 8.75)	0.162
	AG	66	1.00 (0.00, 13.10)	
	GG	24	0.00 (0.00, 2.28)	
rs2075572	GG	19	0.80 (0.00, 5.00)	0.799
	CG	60	0.85 (0.00, 4.80)	
	CC	63	0.90 (0.00, 13.50)	
rs9322447	AA	6	1.20 (0.15, 37.00)	0.505
	AG	56	0.60 (0.00, 4.65)	
	GG	80	0.95 (0.00, 10.38)	

Table 4. *Summary of the adverse reactions for different genotype groups.*

Genotype		N	Vomiting	*P*	Nausea	*P*	Dizziness	*P*
rs1799971	AA	52	11 (21.2%)	0.737	14 (26.9%)	0.844	5 (9.6%)	0.889
	AG	66	15 (22.7%)		16 (24.2%)		6 (9.1%)	
	GG	24	7 (29.2%)		5 (20.8%)		3 (12.5%)	
rs2075572	GG	19	7 (36.8%)	0.274	7 (36.8%)	0.355	2 (10.5%)	0.991
	CG	60	14 (23.3%)		15 (25.0%)		6 (10.0%)	
	CC	63	12 (19.0%)		13 (20.6%)		6 (9.5%)	
rs9322447	AA	6	1 (16.7%)	0.924	3 (50.0%)	0.337	0 (0.0%)	0.703
	AG	56	13 (23.2%)		13 (23.2%)		6 (10.7%)	
	GG	80	19 (23.8%)		19 (23.8%)		8 (10.0%)	

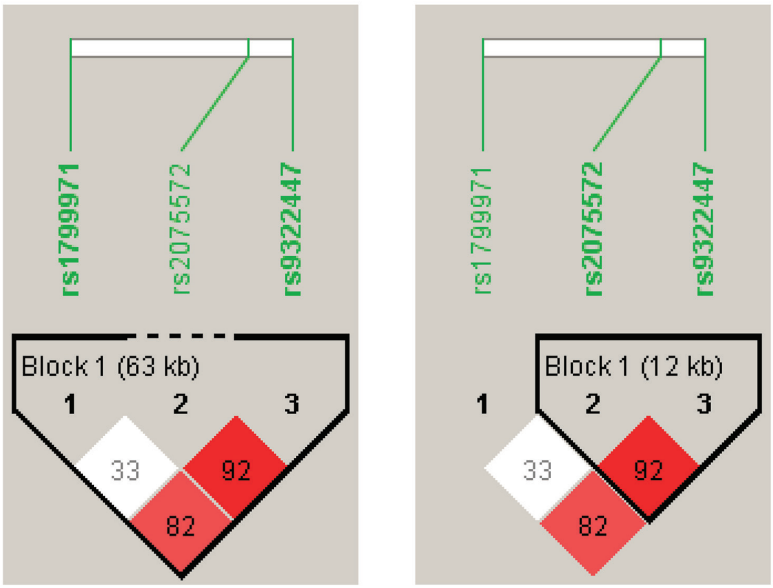

Fig. 3. *A. Construction of OPRM1 haplotype block 1. B. Construction of OPRM1 haplotype block 2.*

Table 5. *Haplotype analysis of OPRM1 SNPs.*

Vomiting	ADR	Normal	*P*	Nausea	ADR	Normal	*P*	Dizziness	ADR	Normal	*P*
Number	33	109		Number	35	107		Number	14	128	
Block 1				Block 1				Block 1			
GG	0.410	0.376	0.619	GG	0.352	0.395	0.599	GG	0.429	0.379	0.739
AG	0.362	0.381	0.822	AG	0.377	0.376	0.980	AG	0.357	0.378	0.896
AA	0.198	0.229	0.836	AA	0.252	0.213	0.604	AA	0.214	0.223	1.000
GA	0.029	0.014	0.548	GA	0.020	0.016	1.000	GA	-	0.019	-
Block 2				Block 2				Block 2			
CG	0.576	0.663	0.374	CG	0.586	0.661	0.494	CG	0.643	0.642	0.987
GA	0.227	0.227	0.836	GA	0.271	0.212	0.604	GA	0.214	0.228	1.000
GG	0.197	0.094	0.119	GG	0.143	0.110	0.853	GG	0.143	0.115	1.000
CA	-	0.016	-	CA	-	0.017	-	CA	-	0.014	-

who were homozygous for the G allele of rs2075572, this indirectly indicates that patients with the G allele of rs2075572 endure higher levels of postoperative pain. Tthe results of this study suggest that rs2075572 and rs9322447 have no effect on average pain intensity, opioids consumption, and ADR. Because of the disunity and the subjectivity of pain assessment, we adopted 2 targets, mean pain intensity and maximal pain intensity. According to the results of our research, the standard of postoperative pain intensity needs further consideration.

Research of opioids consumption found those with the rs1799971 GG genotype need more opioids than those without the GG genotype. But in this study, rs1799971 is irrelevant with opioids consumption and pain intensity according to our results. One possible explanation is that the use of flurbiprofen axetil affects the calculation of opioids consumption, this part of analgesics cannot be counted in total.

Boswell et al (22) found a correlation between pain relief and hydrocodone dose in patients with OPRM1

118 AA. Pain relief in 118A patients did not correlate with serum hydrocodone levels, but rather with serum hydromorphone levels; therefore, researchers recommend measuring serum opioid concentration when assessing the role of OPRM1 variants in pain intensity. This result provides direction for our future study. Most of the research shows that rs1799971 did not affect the pain intensity (VAS score) and ADR; the results are the same as our research.

Based on the LD test result, 2 blocks of haplotype were derived. Block 1 consists of rs1799971 and rs9322447 (LD parameters: D′ = 0.82, r^2 = 0.14), block 2 consists of rs2075572 and rs9322447 (LD parameters: D′ = 0.92, r^2 = 0.51). Last, the results showed that these blocks were irrelevant with ADR.

We didn't investigate the association between rs3745367 with serum resistin levels in this research. Serum resistin levels of incision part should be investigated in future studies; this may increase the possibility of false results.

Our present findings suggest that rs3745367 is an influencing factor for postoperative pain intensity in Chinese patients and the mechanism by how resistin influences postoperative pain remains unclear. Postoperative pain is affected by many factors. Rs2075572 and rs9322447 also affect pain intensity.

Financial Disclosures

Jiangsu Medical Innovation Team (Leading Talents) Project. Project Number: CXTDA2017041.

Contribution

Han Xie contributed to the manuscript preparation. Qingqing Fan performed the data analyses and wrote the manuscript. Zhengliang Ma provided anesthetic support. Zhengxiang Chen provided support in pain management. Qing Shu helped perform the analysis with constructive discussions. Danying Li provided genetics support. Weihong Ge helped design the research.

References

1. Duan G, Xiang G, Zhang X, et al. A single-nucleotide polymorphism in SCN9A may decrease postoperative pain sensitivity in the general population. *The Journal of the American Society of Anesthesiologists* 2013; 118:436-442.
2. Lu L. The impact of genetic variation on sensitivity to opioid analgesics in patients with postoperative pain: A systematic review and meta-analysis. *Pain Physician* 2015; 18:131-152.
3. Motaghedi R, Bae J J, Memtsoudis S G, et al. Association of obesity with inflammation and pain after total hip arthroplasty. *Clin Orthop* 2014; 472:1442-1448.
4. Chen Y W, Lin M F, Chen Y C, et al. Exercise training attenuates postoperative pain and expression of cytokines and N-methyl-D-aspartate receptor subunit 1 in rats. *Region Anesth Pain M* 2013: 38:282-288.
5. Bas S, Finckh A, Puskas G J, et al. Adipokines correlate with pain in lower limb osteoarthritis: Different associations in hip and knee. *Int Ophthalmol* 2014; 38:2577-2583.
6. Lim G, Kim H, McCabe M F, et al. A leptin-mediated central mechanism in analgesia-enhanced opioid reward in rats. *J Neurosci* 2014; 34:9779-9788.
7. Sato H, Muraoka S, Kusunoki N, et al. Resistin upregulates chemokine production by fibroblast-like synoviocytes from patients with rheumatoid arthritis. *Arthritis Res Ther* 2017; 19:263.
8. Calvet J, Orellana C, Giménez N A, et al. Differential involvement of synovial adipokines in pain and physical function in female patients with knee osteoarthritis. A cross-sectional study. *Osteoarthritis Cartilage* 2018; 26:276-284.
9. Rubino E, Vacca A, Govone F, et al. Investigating the role of adipokines in chronic migraine. *Cephalalgia* 2017; 37:1067-1073.
10. Chai N C, Gelaye B, Tietjen G E, et al. Ictal adipokines are associated with pain severity and treatment response in episodic migraine. *Neurology* 2015; 84:1409-1418.
11. Onuma H, Tabara Y, Kawamura R, et al. Plasma resistin is associated with single nucleotide polymorphisms of a possible resistin receptor, the decorin gene, in the general Japanese population. *Diabetes* 2013; 62:649-652.
12. Hozumi J, Sumitani M, Nagashima M, et al. Resistin is a novel marker for postoperative pain intensity. *Anesth Analg* 2019; 128:563-568.
13. Tan E C, Tan C H, Karupathivan U, et al. Mu opioid receptor gene polymorphisms and heroin dependence in Asian populations. *Neuroreport* 2003; 14:569-572.
14. Hwang I C, Park J Y, Myung S K, et al. OPRM1 A118G gene variant and postoperative opioid requirement: A systematic review and meta-analysis. *Anesthesiology: The Journal of the American Society of Anesthesiologists* 2014; 121:825-834.
15. Zahari Z, Lee C S, Ibrahim M A, et al. The opposing roles of IVS2+ 691 CC genotype and AC/AG diplotype of 118A> G and IVS2+ 691G> C of OPRM1 polymorphisms in cold pain tolerance among opioid-dependent Malay males on methadone therapy. *Pain and Therapy* 2015; 4:179-196.
16. Liu J, Hu D, Jiang Y, et al. Association between single nucleotide polymorphisms in the OPRM1 gene and intraoperative remifentanil consumption in northern Chinese women. *Pharmacology* 2014; 94:273-279.

17. Nielsen S, Degenhardt L, Hoban B, et al. A synthesis of oral morphine equivalents (OME) for opioid utilisation studies. *Pharmacoepidem Dr S* 2016; 25:733-737.
18. Calvet J, Orellana C, Giménez N A, et al. Differential involvement of synovial adipokines in pain and physical function in female patients with knee osteoarthritis. A cross-sectional study. *Osteoarthritis Cartilage* 2018; 26:276-284.
19. Bas S, Finckh A, Puskas G J, et al. Adipokines correlate with pain in lower limb osteoarthritis: Different associations in hip and knee. *Int Orthop* 2014; 38:2577-2583.
20. Hivert M F, Manning A K, McAteer J B, et al. Association of variants in RETN with plasma resistin levels and diabetes-related traits in the Framingham Offspring Study. *Diabetes* 2009; 58:750-756.
21. Kawamura R, Tabara Y, Tsukada A, et al. Genome-wide association study of plasma resistin levels identified rs1423096 and rs10401670 as possible functional variants in the Japanese population. *Physiol Genomics* 2016; 48:874-881.
22. Boswell M V, Stauble M E, Loyd G E, et al. The role of hydromorphone and OPRM1 in postoperative pain relief with hydrocodone. *Pain Physician* 2013; 16:E227-E235.