

# Correlation of *P2RX7* gene rs1718125 polymorphism with postoperative fentanyl analgesia in patients with lung cancer

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## Abstract

The aim of this study was to investigate the association between purinergic receptor *P2X7* (*P2RX7*) gene rs1718125 polymorphism and analgesic effect of fentanyl after surgery among patients with lung cancer in a Chinese Han population.

A total of 238 patients with lung cancer who received resection were enrolled in our study. The genotype distributions of *P2RX7* rs1718125 polymorphism were detected by polymerase chain reaction and direct sequencing. Postoperative analgesia was performed by patient-controlled intravenous analgesia, and the consumption of fentanyl was recorded. The postoperative pain was measured by visual analog scale (VAS). Differences in postoperative VAS score and postoperative fentanyl consumption for analgesia in different genotype groups were analyzed by analysis of variance assay.

The frequencies of GG, GA, and AA genotypes were 46.22%, 44.96%, and 8.82%, respectively. After surgery, the postoperative VAS score of GA group was significantly high in the period of analgesia after general anesthesia and at 6 hours after surgery ( $P = .041$  and  $P = .030$ , respectively), while AA group exhibited obviously high in the period of analgesia after general anesthesia ( $P < .001$ ), at postoperative 6 hours ( $P = .006$ ) and 24 hours ( $P = .016$ ). Moreover, the patients carrying GA and AA genotypes needed more fentanyl to control pain within 48 hours after surgery ( $P < .05$  for all).

*P2RX7* gene rs1718125 polymorphism is significantly associated with postoperative pain and fentanyl consumption in patients with lung cancer.

**Abbreviations:** A = adenine, ANOVA = analysis of variance, ASA = American Society of Anesthesiologists, ATP = adenosine triphosphate, BIS = bispectral index, cm = centimeter, G = guanine, h = hour, kg = kilogram,  $\mu\text{g}$  = microgram, min = minute, *P2RX7* = purinergic receptor *P2X7*, PCIA = patient-controlled intravenous analgesia, PCR = polymerase chain reaction, SNPs = single-nucleotide polymorphisms, VAS = visual analog scale.

**Keywords:** analgesics, fentanyl, *P2RX7*, polymorphism, postoperative pain

## 1. Introduction

Lung cancer is a malignant disease which is considered as a leading cause for cancer-related death worldwide.<sup>[1]</sup> Under the combination of environmental factors and competitive pressures, the morbidity of lung cancer is increasing year by year, and the prevention and treatment of lung cancer become a worldwide problem.<sup>[2]</sup> Surgery is the 1st-line treatment for early lung cancer, which is also the basis for comprehensive treatment of lung cancer.<sup>[3]</sup> However, the postoperative pain is always significant

which negatively affect rehabilitation, quality of life, and outcomes of the patients.<sup>[4]</sup> The postsurgical pain management is extremely important for patients with lung cancer.

Opioid drugs are frequently used for pain control in thoracic surgery.<sup>[5]</sup> Fentanyl, a kind of opioid analgesic, has strong analgesic effects, and it does not influence visceral functions.<sup>[6]</sup> However, the analgesic effects of fentanyl may exhibit significant individual differences.<sup>[7]</sup> The individual differences of fentanyl may be attributed to surgical types, age, gender, psychological factors, individual sensitivity to pain, as well as genetic factors.<sup>[8]</sup> Recently, accumulated evidences have suggested that the genetic factors play crucial roles in determining the analgesic effect of fentanyl.

Postoperative pain may be induced by the pronociceptive mediators which are released during operation and tissue injury, such as adenosine triphosphate (ATP), glutamate, kinins, cytokines, and tropic factors.<sup>[9]</sup> The purinergic receptor *P2X7* (*P2RX7*), which is activated by extracellular ATP, takes part in pain regulation.<sup>[10]</sup> *P2X7* receptor could mediate pain sensitivity both through its effects on peripheral tissue injury and its regulation on nervous system processing.<sup>[11]</sup> The alterations in *P2X7* receptor may influence individual sensitivity to postsurgical pain, as well as the analgesic efficacy of opioids. *P2RX7* gene, the encoded gene of *P2X7* receptor, and the genetic single-nucleotide polymorphisms (SNPs) of the gene may hold the capacity to influence *P2X7* receptor function.<sup>[12–14]</sup> Rs1718125 is a widely studied polymorphism of *P2RX7* gene. It has been reported that *P2RX7* rs1718125 SNP could influence cold pain sensitivity and fentanyl consumption in Japanese patients who received painful

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orofacial cosmetic operation.<sup>[15]</sup> But research on the correlation between *P2RX7* gene polymorphisms and analgesic fentanyl after lung cancer surgery is few.

The present study was conducted to investigate the genetic association of *P2RX7* gene rs1718125 polymorphism with the effect of fentanyl after surgery among patients with lung cancer in a Chinese Han population.

## 2. Materials and methods

### 2.1. Ethics statement

This study was approved and consented by the Ethics committee of Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China. The process of sample collection was conducted according to the ethnic criteria of national human genome research. Written informed consent was obtained from each participant or their guardians beforehand. All participants were native Chinese Han population.

### 2.2. Study subjects

A total of 238 patients who had undergone curative resection for lung cancer in Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, School of Medicine, University of Electronic Science and Technology of China were randomly selected in this study. The inclusion criteria were as follows: adult population; diagnosed with lung cancer based on pathological examination; the surgical treatments included lobectomy, bilobectomy, or selective lobectomy; American Society of Anesthesiology (ASA) physical status I and II; and native Chinese Han population, without blood relationship. Additionally, the conditions of the patients met the following criteria would be excluded: with history of psychiatric illness, and severe liver, kidney, or cardiovascular disease; receiving preoperative chemotherapy or radiation therapy; taking opioid analgesic within three months; intraoperative conversion to pneumonectomy or sublobar resection; undergoing a revision surgery within 1 week.

### 2.3. Induction and maintenance of anesthesia

General anesthesia was induced by target-controlled infusion of propofol (0.8  $\mu\text{g}/\text{kg}$ ). For maintenance of anesthesia, all patients were treated with continuous infusion of propofol and fentanyl, intermittent intravenous injection of ammonium bromide. Multifunction computer detector was applied for the detection of the bispectral index (BIS) of the patients under anesthesia. The infusion velocity of propofol and fentanyl was adjusted based on BIS and hemodynamic parameters, respectively. Thirty minutes before the end of surgery, 10  $\mu\text{g}$  fentanyl was injected. The radical operation was performed by the same surgeon team.

### 2.4. Postoperative analgesia

Postoperative analgesia was performed by patient-controlled intravenous analgesia (PCIA) using an automatic infusion pump (Apon, ZZB-300): 1  $\mu\text{g}/\text{kg}$  fentanyl (RenFu Pharmaceutical Co, Ltd, Yi Chang, China). The infusion rate of 1 mL/h, and the lockout time was 15 minutes. Postoperative analgesia was continuously maintained for 72 hours. According to the patients' pain condition, additional intravenous and oral opioids were used. Doses of fentanyl administered were normalized to body weight.

The pain severity of the patients was assessed at 6, 12, 24, and 48 hours postoperatively using a 100-mm visual analog scale (VAS).<sup>[16]</sup> A horizontal line 100 mm in length of VAS was applied for the classification of postoperative pain: no pain (0–4 mm); mild pain (<30 mm); moderate pain (40–60 mm); and severe pain (70–100 mm).

### 2.5. Determination of the polymorphism

Two milliliters peripheral blood sample was collected from each patient before anesthesia using the anti-coagulative tube with EDTA-disodium salt. The genetic DNA samples were extracted from whole blood samples was conducted using Genome DNA extraction kit (TaKaRa, Dalian Biological Engineering Co, Ltd, Dalian, China) according to manufacturer instructions. To analyze the genotype distribution of *P2RX7* gene rs1718125 polymorphism, the mutant region was partially amplified by polymerase chain reaction (PCR). The primer sequences for PCR amplification were as follows: forward: 5'-TCAAGTCCTA-CAGGGTTTCTC-3'; reverse: 5'-GGCTGGTGCTCTTTGGTA-3'. The PCRs were performed in a total volume of 25  $\mu\text{L}$ , including 12.5  $\mu\text{L}$  2 $\times$  Taq PCR master mix, 2  $\mu\text{L}$  primer (1  $\mu\text{L}$  each of upstream and downstream), 2  $\mu\text{L}$  genomic DNA, and 8.5  $\mu\text{L}$  ddH<sub>2</sub>O. The PCR procedures consisted of an initial denaturation at 94°C for 7 minutes, followed by 40 cycles of 94°C for 30 seconds, annealing at 55°C for 30 seconds, 72°C for 60 seconds, and a final extension of 72°C for 10 minutes.

The PCR products were detected by 2% agarose gel electrophoresis, and identified under ultraviolet light. The identification of rs1718125 SNP was conducted using direct sequencing by automated DNA sequencing with an Applied Biosystems 3730xl automated sequencer (Applied Biosystems, Foster City, CA), and the sequence analysis was performed using Vector NTI software.

### 2.6. Statistical analysis

All the data analyses were performed using PASW Statistics 18.0 statistical software (SPSS Inc, Chicago, IL). The continuous data were expressed as mean  $\pm$  standard deviation, and their comparison between groups was analyzed using Student *t* test or analysis of variance. Chi-squared test was applied to compare the categorical variables between groups. All the analyses were 2 sided, and *P*-value < .05 was considered as statistically significant.

## 3. Results

### 3.1. Clinical characteristics and genotyping

A total of 238 patients with lung cancer were recruited in this study, including 145 males and 93 females. According to ASA classification, 147 patients were graded at stage I, while stage II included 91 patients. The average age of the study population was 56.67  $\pm$  9.17 years. The mean weight of the patients with lung cancer was 59.91  $\pm$  8.36 kg, and their average height was 166.63  $\pm$  6.95 cm. The average operation time of the study population was 143.84  $\pm$  34.81 minutes, and the analgesia time was 182.04  $\pm$  33.05 minutes. During the operation, the mean fentanyl injection was 236.07  $\pm$  53.64  $\mu\text{g}$  (Table 1).

According to the genotyping results, 3 genotype groups were detected for *P2RX7* gene rs1718125 polymorphism in the study population. The genotype and allele frequencies are summarized in Table 2. It was noted that homozygous wild (GG) was found in 110 (46.22%) patients, while heterozygous mutant (GA) in 107

**Table 1**  
The demographic and clinical characteristics of the study population.

Characteristics	Case
Total number	238
Age, yr	56.67 ± 9.17
Gender, male/female	145/93
Weight, kg	59.91 ± 8.36
Height, cm	166.63 ± 6.95
Duration of operation, min	143.84 ± 34.81
Duration of analgesia, min	182.04 ± 33.05
Intraoperative fentanyl, µg	236.07 ± 53.64
ASA classification, I/II	147/91

ASA = American Society of Anesthesiologists, cm = centimeter, kg = kilogram, µg = microgram, min = minute.

(44.96%) patients and homozygous mutant (AA) in 21 (8.82%) patients. Additionally, the minor allele (A) frequency of rs1718125 polymorphism in the present study was 31.30%.

In addition, we compared the baseline characteristics of the study population according to their genotypes of rs1718125 polymorphism. There were no significant differences among the 3 genotypes in gender, age, weight, height, ASA classification, and duration of surgery and anesthesia ( $P > .05$  for all) (Table 3).

### 3.2. Postoperative VAS score

The comparison of VAS score among the GG, GA, and AA genotype group during postoperative PCIA period is displayed in Table 4. Compared with GG genotype group, the postoperative VAS score of GA group was significantly higher in the period of analgesia after general anesthesia and at 6 hours after surgery ( $P = .041$  and  $P = .030$ , respectively). The patients carrying AA genotype also showed high VAS scores in the period of analgesia after general anesthesia ( $P < .001$ ), at postoperative 6 hours ( $P = .006$ ) and 24 hours ( $P = .016$ ), in comparison with GG genotype. No significant difference was observed in VAS scores at postoperative 48 hours ( $P > .05$  for both).

### 3.3. Fentanyl consumption

We also compared the postoperative cumulative amount of fentanyl among the GG, GA and AA genotype group during postoperative PCIA period. At 6, 24, and 48 hours after the surgery, the fentanyl consumption of the AA and GA genotype groups was significantly higher than that of the GG genotype group ( $P < .05$  for all) (Table 5). The patients with lung cancer carrying GA and AA genotypes needed more fentanyl to control pain after surgical treatments.

**Table 2**  
The genotype and allele frequencies of P2RX7 gene rs1718125 polymorphism in the study sample.

	GG	GA	AA	G	A
Number	110	107	21	327	149
Frequency, %	46.22	44.96	8.82	68.70	31.30

AA = adenine/adenine, GA = guanine/adenine, GG = guanine/guanine, P2RX7 = purinergic receptor P2X 7.

**Table 3**  
Comparison of demographic and clinical characteristics among rs1718125 3 genotypes in patients with lung cancer.

	GG	GA	AA	P
Case, n	110	107	21	–
Age, yr	56.78 ± 8.59	56.26 ± 9.93	58.14 ± 8.20	.682
Sex, male/female	67/43	65/42	13/8	.995
Weight, kg	61.25 ± 7.93	58.85 ± 8.73	58.29 ± 7.96	.068
Height, cm	165.75 ± 7.60	167.15 ± 6.22	168.62 ± 6.58	.129
Duration of operation, min	149.43 ± 32.39	140.01 ± 38.32	144.34 ± 34.74	.111
Duration of analgesia, min	186.37 ± 29.38	178.11 ± 38.07	179.33 ± 19.09	.170
Intraoperative fentanyl, µg	239.45 ± 56.25	239.09 ± 50.54	213.33 ± 48.21	.104
ASA classification, I/II	67/43	68/39	12/9	.832

AA = adenine/adenine, ASA = American Society of Anesthesiologists, cm = centimeter, GA = guanine/adenine, GG = guanine/guanine, kg = kilogram, µg = microgram, min = minute.

**Table 4**  
Postoperative VAS score in different groups ( $\bar{x} \pm s$ ).

Time	Groups			P1	P2
	GG	GA	AA		
Analgnesia after general anesthesia	5.59 ± 1.55	6.09 ± 1.50	7.38 ± 1.16	.041	<.001
Postoperative 6 h	3.72 ± 1.39	4.23 ± 1.42	4.81 ± 1.97	.030	.006
Postoperative 24 h	2.73 ± 0.88	2.99 ± 1.17	3.43 ± 1.29	.168	.016
Postoperative 48 h	1.80 ± 0.58	1.91 ± 0.89	2.14 ± 0.75	.530	.141

AA = adenine/adenine, GA = guanine/adenine, GG = guanine/guanine, h = hour, P1 = GA vs GG, P2 = AA vs GG, VAS = visual analog scale.

**Table 5****Postoperative fentanyl consumption in 3 groups ( $\bar{x} \pm s$ ).**

Time	Groups				
	GG	GA	AA	P1	P2
Postoperative 6 h, $\mu\text{g}/\text{kg}$	4.51 $\pm$ 1.54	6.53 $\pm$ 1.32	8.01 $\pm$ 1.94	<.001	<.001
Postoperative 24 h, $\mu\text{g}/\text{kg}$	9.27 $\pm$ 3.06	10.45 $\pm$ 2.99	11.69 $\pm$ 3.40	.013	.003
Postoperative 48 h, $\mu\text{g}/\text{kg}$	11.51 $\pm$ 2.95	12.71 $\pm$ 3.55	13.72 $\pm$ 3.35	.020	.013

$\mu\text{g}$ =microgramme, AA=adenine/adenine, GA=guanine/adenine, GG=guanine/guanine, h=hour, kg=kilogram, P1=GA vs. GG, P2=AA vs. GG.

#### 4. Discussion

Postoperative pain is a series of physiologic, psychologic, and behavioral responses to the surgical stimulation, and is a frequently observed postoperative complication which could affect the prognosis of patients and the life quality.<sup>[17]</sup> Postoperative analgesia is quite important to improve the life quality and the prognosis of patients.<sup>[18]</sup> But even with postoperative analgesic treatments, approximate 50% of patients still suffer from severe pain within 24 hours after surgery.<sup>[19]</sup> The unsatisfactory analgesic effects may be attributed to individual differences in pain perception and/or analgesic sensitivity.

Fentanyl is one of the most commonly used opioid drugs, which is always used for preoperative, intraoperative, and postoperative analgesia, as well as the treatment of terminal cancer.<sup>[20]</sup> However, the significantly individual sensitivities to fentanyl remains a great challenge in clinic. Recently, accumulating studies have demonstrated that the genetic mutations are closely associated with analgesic effects of fentanyl.<sup>[21,22]</sup> Several SNPs have been confirmed to influence postoperative fentanyl analgesia, such as *CYP3A4\*1G*, *CGRP 4218T/C*, *UGT2B7*, rs7439366, rs4587017, rs1002849, etc.<sup>[23–25]</sup> In this study, we investigated the genetic effects of *P2RX7* rs1718125 polymorphism on analgesic effects of fentanyl in patients with lung cancer after resections.

The P2X7 receptor is a nonselective cation channel which plays important roles in various biologic processes, including inflammatory response, cell growth and death, metabolic event, and nervous system processing.<sup>[26]</sup> In recent, P2X7 receptor has been reported to be involved in modulation of pain.<sup>[11]</sup> *P2RX7* gene, the encoding gene of P2X7 receptor, is highly polymorphic. In the present study, we analyzed the relationship between *P2RX7* gene rs1718125 polymorphism and postoperative pain sensitivity and fentanyl consumption in 238 patients with lung cancer who received lung resection treatment. PCIA was performed for pain control in the study population. The frequency of minor allele of rs1718125 polymorphism was up to 31.30% in Chinese Han population. The results were in consistent with the 1000 Genomes Project. We found that the patients carrying GA and AA genotypes underwent high VAS scores, compared with GG genotype. The patients carrying GA and AA genotypes showed sensitivity to pain, and they had strong pain perception after resections. The alterations might affect the inflammatory response of the injury tissues and nervous system processing, thus influencing individual pain tolerance.<sup>[11]</sup> However, the underlying molecular mechanisms had not been explored in present study. Further investigations are required to address the issues.

In addition, we analyzed the postoperative consumption of fentanyl among the study population based on their genotypes of *P2RX7* gene rs1718125 polymorphism. Analysis results suggested that the fentanyl consumption of the AA and GA genotype groups was significantly higher than that of the GG genotype

group within 48 hours after operation. The patients with GA and AA genotypes needed more fentanyl to control postoperative pain. The conclusion was consistent with the previous reports. The study carried out by Ide et al reported that the patients with rs1718125 mutational genotypes showed high sensitivity to cold pain. Moreover, the SNP might influence analgesic effects of opioids for acute cold pain in Japanese population.<sup>[15]</sup>

There were still several limitations in present study. Firstly, the sample size was relatively small. Secondly, the underlying mechanisms of *P2RX7* gene polymorphism in postoperative pain and the analgesic effect of fentanyl remained poorly known. Thirdly, the primary study proved that genetic variants in *P2RX7* do influence pain sensitivity and analgesic effect of fentanyl among patients with lung cancer. Due to the short study duration, only 1 SNP was selected in our study. Further investigations are required to explore the roles of other SNPs in *P2RX7* gene or other genes in postoperative pain. Additionally, postoperative pain is a complex process which may be regulated by various genes. However, only gene and a single polymorphism were studied in our study. The interaction between *P2RX7* gene rs1718125 polymorphism and other SNPs or genes had not been investigated in our study. Thus, further well-designed studied with a larger sample size will be performed to verify and improve our conclusions.

In conclusion, *P2RX7* gene rs1718125 polymorphism is associated with the pain sensitivity and analgesic effect of fentanyl after surgery among patients with lung cancer in Chinese Han population. The patients carrying GA and AA genotypes are more likely to show high VAS scores, and need more fentanyl to control pain.

#### Author contributions

**Conceptualization:** Jin Ma, Kexian Zhang.

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