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Association between the rs7583431 single nucleotide polymorphism close to the activating transcription factor 2 gene and the analgesic effect of fentanyl in the cold pain test

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Abstract

Background: Activating transcription factor 2 (ATF2) is a member of the leucine zipper family of DNA binding proteins and is widely distributed in tissues. Several recent studies have demonstrated that this protein is involved in mechanisms that are related to pain and inflammation. However, unclear is whether polymorphisms of the *ATF2* gene, which encodes the human ATF2 protein, influence pain or analgesic sensitivity. This study examined associations between the analgesic effect of fentanyl in the cold pressor-induced pain test and polymorphisms in the *ATF2* gene in 355 Japanese subjects.

Results: In this study, 33 single nucleotide polymorphisms (SNPs) were selected, and a total of 2 linkage disequilibrium blocks with 6 Tag SNPs (rs1153702, rs7583431, rs2302663, rs3845744, rs268214, and rs1982235) were observed in the region within and around the *ATF2* gene. We further analyzed associations between these Tag SNPs and clinical data. Even after multiple testing with Bonferroni adjustments, an increase in the analgesic effect of fentanyl in the cold pressor-induced pain test was significantly associated with a greater number of the A allele of the rs7583431 SNP (linear regression, $P = .001$).

Conclusions: The present findings may contribute to adequate pain relief in individual patients. Although more research on the genetic factors that influence opioid sensitivity is needed, analgesic requirements may be predicted by analyzing *ATF2* SNPs, together with other polymorphisms of genes that are reportedly associated with opioid sensitivity, such as *CREB1*, *OPRM1*, and *GIRK2*.

KEYWORDS
analgesia, *ATF2*, cold pain, fentanyl, polymorphism

Aoki and Nishizawa contributed equally.

1 | INTRODUCTION

Opioid analgesics are widely used for the treatment of moderate-to-severe pain during the perioperative period and in palliative care, although analgesic efficacy is well known to vary widely among individuals. Both environmental and genetic factors are involved in individual differences in opioid sensitivity.[1] The influence of environmental factors, such as surgical factors, preoperative pain factors, demographics, and psychological factors, can be controlled by the study design, but the influence of genetic factors is not as easily controlled.[2] To date, associations between several gene polymorphisms and fentanyl efficacy were reported.[3,4] The present study explored possible associations between the analgesic efficacy of fentanyl and single nucleotide polymorphisms (SNPs) near the activating transcription factor 2 (*ATF2*) gene region.[5]

Our recent study found that the rs2952768 SNP, which is located close to the *CREB1* gene, was associated with CREB1 mRNA expression and opioid sensitivity.[6] The *CREB1* gene is located relatively close to the *ATF2* gene region (2q31-33). Activating transcription factor 2 (ATF2; previously called CREB2) is categorized as a member of the cyclic adenosine monophosphate responsive element-binding protein (CREB) family. Similar to *CREB1*, *ATF2* gene encodes an activating transcription factor that is a CRE-binding transcription factor. ATF2 is a member of the leucine zipper family of DNA binding proteins and is widely distributed in tissues, including the liver, lung, spleen, and kidney.[7] ATF2 is also expressed in the cytoplasm at the outer mitochondrial membrane.[7] Although ATF2 functions differently from CREB1 in the signaling pathway, Crohn's disease was shown to be associated with CREB1 and ATF2 through deleted in malignant brain tumor 1 (*DMBT1*) gene expression.[8] Moreover, the interplay between CREB1 and ATF2 was related to the progression of prostate cancer.[9] Since a 1996 study reported that ATF2-deficient mice were chondrodysplasic and presented neurological abnormalities,[10] ATF2 has been more widely investigated. Several recent studies demonstrated that this protein is involved in mechanisms that are related to pain and regulated by p38 mitogen-activated protein kinase in inflammation.[5] However, unclear is whether polymorphisms of the *ATF2* gene, which encodes the human ATF2 protein, influence pain or analgesic sensitivity.

2 | MATERIALS AND METHODS

2.1 | Patients

The protocol for this research project was approved by the Ethics Committees of Tokyo Dental College and the Tokyo Metropolitan Institute of Medical Science (approval no. 086 and 15-6, respectively) and conformed with the provisions of the Declaration of Helsinki. Written informed consent was obtained from all of the patients and from the parents if the patient was younger than 20 years old. Enrolled in the study were 355 healthy patients (American Society of Anesthesiologists Physical Status I, 15-52 years old, 126 males and 229 females) who were scheduled to undergo orthognathic surgery (ie, bilateral mandibular sagittal split ramus osteotomy) for mandibular prognathism at Tokyo Dental College Suidobashi Hospital. Patients were excluded preoperatively if they had a history of acute or chronic kidney injury, drug abuse, or chronic pain or were unable to use the intravenous patient-controlled analgesia (IV-PCA) device.

2.2 | Cold pressor-induced pain test

The temperature in the operating room was maintained at 26°C. Crushed ice cubes and cold water were blended 15 minutes before testing in a 5-L isolated tank, and the mixture was stirred immediately before the test to ensure uniform temperature distribution (0°C) within the tank. The dominant hand was immersed up to the hand and wrist because the nondominant hand is where the venous line was inserted. Blood pressure was not measured during the cold pressor-induced pain test. The patients were instructed to keep the hand calm in the ice-cold water and withdraw it as soon as they perceived any pain. A cutoff point of 150 seconds was set to avoid tissue damage.

The patients first underwent the cold pressor-induced pain test before analgesic administration (PPL-pre). The dominant hand was removed from the ice water and warmed with a hair dryer as soon as PPL-pre was measured. After the sensation of cold was completely abolished, the patients received 2 μg/kg fentanyl through their intravenous line. Three minutes after administration, they underwent the cold pressor-induced pain test again with the same dominant hand to determine PPL-post. The analgesic effect of fentanyl in the preoperative cold pressor-induced pain test was evaluated as the difference between PPL-pre and PPL-post.[11,12]

2.3 | Anesthesia and surgery

The patients were orally premedicated with 5 mg diazepam and 150 mg famotidine 90 minutes before the induction of anesthesia. General anesthesia was induced with propofol at a target blood concentration of 4-6 μg/mL using a target-controlled infusion (TCI) pump (TE-317, Terumo, Tokyo, Japan). Vecuronium (0.1 mg/kg) was administered to facilitate nasotracheal intubation (Portex; inner diameter, 6.5-8.0 mm; Smiths Medical Japan, Tokyo, Japan) and maintained at 0.08 mg/kg/h during surgery. Whenever systolic blood pressure or heart rate increased more than 20% over baseline during surgery, fentanyl was intravenously administered at 1 μg/kg.

The lungs were ventilated with oxygen-enriched air. All of the patients received local anesthesia at the surgical sites with 8 mL of 2% lidocaine that contained 12.5 μg/mL epinephrine.

2.4 | Postoperative pain management

At the end of surgery, 50 mg rectal diclofenac sodium and 8 mg intravenous dexamethasone were administered to prevent postoperative orofacial edema/swelling. After emergence from anesthesia and tracheal extubation, 1.25 mg droperidol was intravenously administered to prevent nausea/vomiting, and IV-PCA with 20 μg/mL fentanyl commenced using a CADD-Legacy PCA pump (Smiths Medical Japan, Tokyo, Japan). Droperidol (0.1 mg/mL) was co-administered with

fentanyl to prevent nausea/vomiting because of a high incidence (up to 30%) of nausea/vomiting with PCA fentanyl in young females. A bolus dose of fentanyl of 20 μg on demand and a lockout time of 10 minutes were set. Continuous background infusion was not employed. Patient-controlled analgesia was continued for 24 hours postoperatively. In the case of refractory adverse effects or inadequate analgesia, PCA with fentanyl was discontinued, and 50 mg rectal diclofenac sodium was prescribed as a rescue analgesic as required.

Postoperative fentanyl use (μg/kg) for 24 h, standardized by body weight, was calculated based on PCA pump records. The intensity of spontaneous pain was assessed 3 and 24 hours postoperatively using a 100-mm visual analog scale (VAS), with 0 mm indicating no pain and 100 mm indicating the worst pain imaginable.

2.5 | Genotyping and linkage disequilibrium analysis

After genomic DNA was extracted from whole-blood samples using standard procedures, whole-genome genotyping was performed using the Infinium assay II with an iScan system (Illumina, San Diego, CA, USA) according to the manufacturer's instructions. The genotype data were evaluated as detailed in our previous report.[6] Briefly, the data for the whole-genome genotyped samples were analyzed using BeadStudio or GenomeStudio with Genotyping module v3.3.7 (Illumina) to evaluate the quality of the results. The genotype data from all 5 BeadChips were merged to analyze all of the samples simultaneously (ie, only the markers that were common to all of the BeadChips were included in the analysis, and the others were automatically excluded). In the data-cleaning process, the samples with a genotype call rate of <0.95 were excluded from further analyses. As a result, 1 sample was excluded from further analyses. Markers with a genotype call frequency of <0.95 or "Cluster sep" (ie, an index of genotype cluster separation) of <0.1 were excluded from the subsequent association study. A total of 295 036 SNP markers survived the filtration process and were used for the GWAS. Linkage disequilibrium (LD) analysis was then performed for 126 samples using Haploview v. 4.1.[13]

To initially analyze SNPs within and around the *ATF2* gene region, the genotype data for all of the SNP markers with *ATF2* gene annotation were extracted among the entire genotype data for approximately 300 000 SNP markers that resulted from whole-genome genotyping.

Of the 39 SNPs with minor allele frequencies above 0.001 that were located within the exon and intron regions and approximately within the 20 kbp 5′- and 3′-flanking regions of the *ATF2* gene, SNPs for the association studies were selected. To identify relationships between the SNPs that were used in the study, an LD analysis was performed for 126 samples among the entire 355 samples using Haploview v. 4.1.[13] To estimate the LD strength between the SNPs, the commonly used D' and r^2 values were pairwise calculated using the genotype dataset of each SNP. Linkage disequilibrium blocks were defined among the SNPs with minor allele frequencies above 0.05 that showed "strong LD" based on the default algorithm of Gabriel et al[14], in which the upper and lower 95% confidence limits on D′ for strong LD were set at 0.98 and 0.7, respectively. Tag SNPs in the LD block were consequently determined using the Tagger software package with default settings, which is incorporated in Haploview and has been detailed in a previous report.[6]

2.6 | Statistical analysis

Prior to the analyses, postoperative fentanyl use for 24 hours was natural-log-transformed for approximation to the normal distribution as described in our previous study.[6] Additionally, the quantitative values of the analgesic effect of fentanyl in the preoperative cold pressor-induced pain test, evaluated as the difference between PPL-pre and PPL-post (in seconds), and 3 and 24 hours postoperative VASs were similarly natural-log-transformed.

Associations between the Tag SNPs and the natural-log-transformed clinical data were analyzed using linear regression. All of the statistical tests were performed using SPSS 19.0 software (SPSS, Chicago, IL, USA). The threshold for statistical significance was $P < .05$. The correction for multiple testing was performed using Bonferroni adjustments. The genotype distributions were checked using the chi-square test, and the absence of significant deviation from the theoretical distribution that is expected from Hardy-Weinberg equilibrium was confirmed.

3 | RESULTS

In the present study, 33 SNPs were selected, and a total of 2 LD blocks with 6 Tag SNPs (rs1153702, rs7583431, rs2302663, rs3845744, rs268214, and rs1982235) were observed in the region within and around the *ATF2* gene (Figures 1 and 2). We further analyzed associations between these Tag SNPs and the clinical data (Table S1). After correcting for multiple testing using Bonferroni adjustments, an increase in the analgesic effect of fentanyl in the cold pressor-induced pain test was significantly associated with a greater copy number of the A allele of the rs7583431 SNP (linear regression; $\beta = -0.184$, $P = .001$; Table S2). The frequency of the minor A allele of the rs7583431 SNP was 0.3704. The medians (variances) for the AA, AC and CC genotypes were 2.773 (2.013), 2.398 (2.765) and 2.398 (3.575), respectively (Figure 3).

PPL-pre, postoperative fentanyl use for 24 hours, and 3 and 24 hours postoperative VASs were not significantly associated with this SNP (linear regression; $\beta = -0.055$, $P = .300$, $\beta = -0.057$, $P = .284$, $\beta = -0.003$, $P = .949$, and $\beta = -0.061$, $P = .248$, respectively).

The genotype distribution of the rs7583431 SNP was checked using the chi-square test, and the absence of significant deviation from the theoretical distribution that is expected from Hardy-Weinberg equilibrium was confirmed ($\chi^2 = 2.3324$, $P = .127$).

4 | DISCUSSION

Initially, genotype data were analyzed for SNPs within and around the *ATF2* gene region. For the 33 SNPs that were selected in this region,

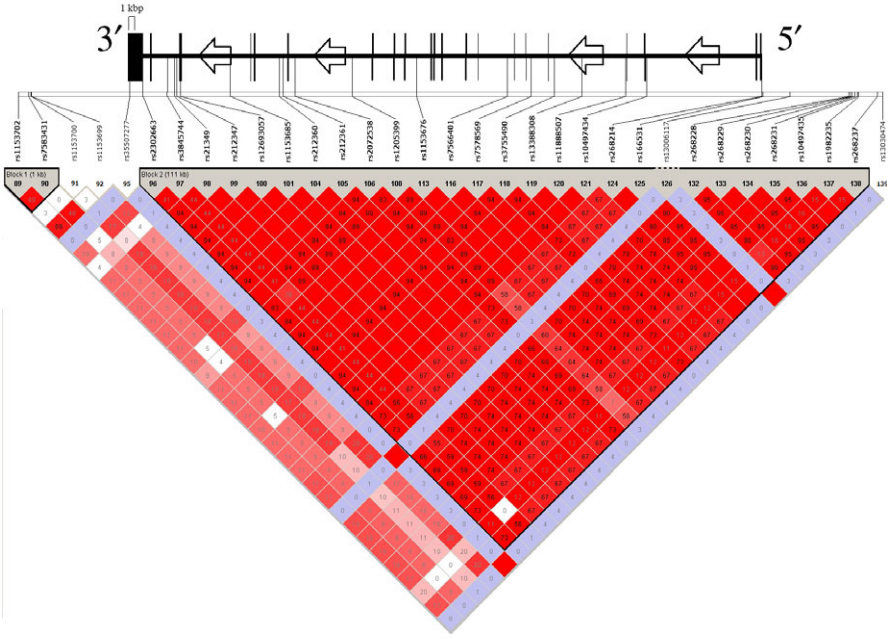

FIGURE 1 State of linkage disequilibrium (LD) between the single nucleotide polymorphisms (SNPs) in the region within and around the *ATF2* gene (LD Plot-r^2). The figure depicts LD relationships between the SNPs in the genomic position from 175 050 000 to 175 190 000 on chromosome 2 in the National Center for Biotechnology Information (NCBI) database (http://www.ncbi.nlm.nih.gov/gene/1386), based on the genotype data of the subjects who underwent orthognathic surgery. Numbers in squares in which 2 SNPs face represent the percentage of the r^2 values that were calculated from the genotype data of the SNPs. The solid horizontal line above the LD plot represents the *ATF2* gene, which is located from 175 072 250 to 175 168 206 (accession no. NM_001256092.1). Solid vertical lines represent the exon regions. The arrows represent the direction of transcription

FIGURE 2 Tag single nucleotide polymorphisms (SNPs) in each linkage disequilibrium (LD) block and haplotype frequencies. Upper numbers are SNP numbers that correspond to those presented in Figure 1 from genomic position 175 050 000 to 175 190 000 on chromosome 2 (http://www.ncbi.nlm.nih.gov/gene/1386). Inverted solid triangles show 6 Tag SNPs that represent the SNPs in each LD block depicted in Figure 1. The numbers beside each haplotype represent the values of each haplotype frequency calculated by Haploview. In the crossing area, a value of multiallelic D' computed for the haplotypes currently displayed is shown, which represents the level of recombination between the 2 blocks

LD analysis was conducted. A total of 2 LD blocks were observed, and 6 Tag SNPs were selected. Among these, the rs7583431 SNP (1 of the 6 Tag SNPs) was associated with the analgesic effect of fentanyl in the preoperative cold pressor-induced pain test.

ATF proteins are well known as procarcinogenic factors in tumors of the prostate, breast, liver, and lung.[7] Some reports indicate the involvement of CREB and the cAMP pathway in the analgesic and rewarding effects of opioids.[15–18] Moreover, our previous study reported that higher mRNA expression levels of the *CREB1* gene in subjects with the C/C genotype of the rs2952768 SNP, identified in a GWAS, may indicate elevated CREB function and lower sensitivity to the rewarding effects of opioids, resulting in greater postoperative opioid analgesic requirements and less vulnerability to dependence on other drugs.[6] Activated ATF2 complexes have recently been reported to stimulate the transcription of various genes that are implicated in inflammation, such as cell adhesion molecules, pro-inflammatory cytokines, and chemokines, and ATF2 activation is evident in several inflammatory diseases, including inflammatory pain.[7] Although the rs7583431 SNP is located 14.6 kbp upstream of the *ATF2* gene region and 23.4 kbp downstream of *RPL21p31* (ribosomal protein L 21 pseudogene 31), this SNP that was included in the LD block might influence the *ATF2* gene. A greater number of the A allele of the rs7583431 SNP were associated with an increase in the analgesic effect of fentanyl in the cold pressor-induced pain test. However, long-term data (eg, postoperative fentanyl use for 24 hours and 3 and 24 hours postoperative VASs) were not significantly associated with this SNP. In our previous study, polymorphisms of the *UGT2B7* gene were not

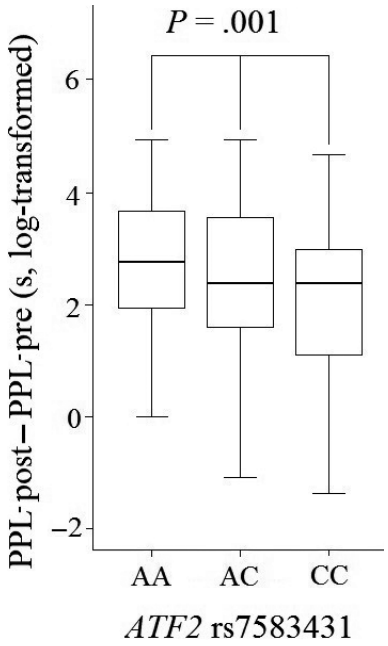

FIGURE 3 Association between rs7583431 single nucleotide polymorphism and the analgesic effect of fentanyl in the preoperative cold pressor-induced pain test. The data are expressed as box and whisker plots. The upper and lower ends of the boxes represent the 75th and 25th percentiles, respectively. Whiskers represent the 90th and 10th percentiles. The median is depicted by the solid line in the box. The analgesic effect fentanyl in the preoperative cold pressor-induced pain test was found to be significantly greater as the number of the A allele increased (linear regression, $P = .001$)

associated with fentanyl sensitivity for severe postoperative pain, but SNPs of *UGT2B7* were associated with fentanyl sensitivity in the cold pressor-induced pain test.[13] Likewise, the rs7583431 SNP of *ATF2* was unrelated to postoperative fentanyl sensitivity for severe postoperative pain but was related to preoperative fentanyl sensitivity for slight preoperative pain. The analgesic effect of fentanyl was significantly associated with an *ATF2* SNP in the present study. Long-term data, such as 3 and 24 hours postoperative pain, might be influenced not by SNPs of *ATF2*[19] but rather by SNPs of other genes, some of which might be related to drug metabolism and excretion.

The present findings may contribute to adequate fentanyl use for pain relief in individual patients. Although more research on the genetic factors that influence opioid sensitivity is needed, adequate fentanyl dosages, especially during the induction of general anesthesia, may be predicted by analyzing *ATF2* SNPs.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

DN and KI conceived the study and designed the experiments. YA and DN performed the statistical analyses and wrote the manuscript. KY, KT, and YK performed the anesthesia and collected the clinical data. SK and JH performed the genotyping procedures. TI, MH, KF, and KI supervised the experiments and finalized the manuscript. All of the authors contributed to writing the manuscript, and all of the authors read and approved the final manuscript.

DATA REPOSITORY

Data are provided as Data S1.

APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

The protocol for this research project was approved by the Ethics Committees of Tokyo Dental College and the Tokyo Metropolitan Institute of Medical Science and conformed with the provisions of the Declaration of Helsinki.

INFORMED CONSENT

Written informed consent was obtained from all of the patients and from the parents if the patient was younger than 20 years old.

REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

Approval no. 086 and 15-6 for Tokyo Dental College and for Tokyo Metropolitan Institute of Medical Science, respectively.

ANIMAL STUDIES

n/a.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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