



# Association between rs2275913 single-nucleotide polymorphism of the *interleukin-17A* gene and perioperative analgesic use in cosmetic orthognathic surgery

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## Funding information

Japan Agency for Medical Research and Development (AMED) Grant/Award Number: JP17dk0307071, JP17ek0610011, JP17mk0101076; MEXT KAKENHI Grant/Award Number: 15H01303, 16H06276, 16K15565, 17H04324, 17K08970, 17K09052, 22790518, 23390377, 24659549, 24790544, 25116532, 26293347, 26860360; Ministry of Health, Labour and Welfare (MHLW) of Japan Grant/Award Number: 14524680, H21-3jigan-ippan-011, H22-lyaku-015, H25-lyaku-020, H26-Kakushintekigan-ippan-060; Smoking Research Foundation (Tokyo, Japan); Astellas Foundation for Research on Metabolic Disorders (Tokyo, Japan)

## Abstract

**Aim:** Interleukin-17A (IL-17A) plays an essential role in tissue inflammation by inducing proinflammatory cytokine and chemokine production and is related to innate immune reactions. IL-17A also contributes to neuroinflammation, neuropathic pain, and mechanical hypersensitivity after peripheral nerve injury in rodents. To clarify the contribution of IL-17A to pain-related phenotypes in humans, we investigated the association between pain-related phenotypes and the rs2275913 single-nucleotide polymorphism (SNP) of the *IL-17A* gene, which has been reported to be associated with rheumatoid arthritis, ulcerative colitis, and some cancers.

**Methods:** The present study used a correlational design to examine the impact of the rs2275913 SNP on postoperative pain-related phenotypes in a group of patients who underwent cosmetic orthognathic surgery.

**Results:** Carriers of the AA genotype had higher opioid requirements during and after surgery than carriers of the AG and GG genotypes ( $P = .009$ ). Linear regression analysis indicated that opioid requirements linearly increased as the copy number of the A allele of the SNP increased ( $P = .008$ ).

**Conclusions:** Opioid requirements during and after surgery are enhanced in carriers of the AA genotype of the rs2275913 SNP of the *IL-17A* gene, possibly through an enhancement of IL-17A function that induces inflammation that is related to the inflammatory pain stimulus.

## KEYWORDS

analgesics, human, IL17A protein, opioid, orthognathic surgery, pain, polymorphism, postoperative, single-nucleotide

Ohka and Nishizawa contributed equally to this work.

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## 1 | INTRODUCTION

Orthognathic surgery has been reported to induce the highest pain intensities among surgeries that cause postoperative pain.<sup>1</sup> In orthognathic surgery, postoperative pain is related to both somatic and neuropathic pathophysiology. Proinflammatory cytokines are associated with somatic pain.<sup>2</sup> Furthermore, neuropathic pain alters the expression of cytokines and cytokine receptors.<sup>3</sup> Thus, inflammatory systems likely engage severe postoperative pain through both somatic and neuropathic components. To control severe postoperative pain after surgery, such as orthognathic surgery, pain-related inflammatory mechanisms need to be clarified.

Interleukin-17A (IL-17A) is a member of the IL-17 cytokine family. Th17 cells, a subset of T helper cells, play important roles in adaptive and innate immunity. Th17 cells secrete proinflammatory IL-17 family cytokines, including IL-17A. IL-17A plays the most prominent role among 6 IL-17 family members in innate immune reactions, such as autoimmune disease, protection from microbial infection, and allergic reactions.<sup>4</sup> Furthermore, IL-17A has been reported to contribute to neuroinflammation, neuropathic pain, and mechanical hypersensitivity after peripheral nerve injury in rodents,<sup>5–7</sup> but unknown is whether such findings translate to humans.

The *IL-17A* gene encodes IL-17A. The rs2275913 single-nucleotide polymorphism (SNP) is located in the 2KB upstream region of the *IL-17A* gene on chromosome 6p12. The rs2275913 SNP is located in the promoter region of the *IL-17A* gene, and the A allele of rs2275913 is associated with higher promoter activity of the *IL-17A* gene.<sup>8</sup> The AA genotype of the rs2275913 SNP of the *IL-17A* gene is reportedly associated with a higher risk of asthma, bronchiolitis,<sup>9</sup> ulcerative colitis,<sup>10</sup> digestive cancer,<sup>11</sup> gastric cancer,<sup>11–13</sup> and cervical cancer.<sup>13</sup> Other studies reported that the rs2275913 SNP had no association with pediatric systemic lupus erythematosus disease activity<sup>14</sup> or cervical cancer<sup>15</sup> and had opposite effects on rheumatoid arthritis,<sup>16</sup> post-bronchiolitis asthma at 11–13 years of age<sup>17</sup> and colorectal cancer.<sup>13</sup> Overall, the AA genotype of the rs2275913 SNP appears to contribute to greater inflammation, leading to autoimmune-related inflammatory diseases, including cancer. Thus, the rs2275917 SNP may reflect the autoimmune-related function of IL-17A. With regard to the function of IL-17A in preventing infection, the AA genotype of the rs2275913 SNP was shown to be associated with protection against tuberculosis but also higher disease severity,<sup>18</sup> hepatitis B virus (HBV) resistance,<sup>19</sup> and *Bacillus Calmette–Guérin* (BCG) osteitis after vaccination.<sup>20</sup> These findings indicate that the AA genotype of the rs2275913 SNP has advantages for preventing infections, whereas this genotype overall leads to more severe inflammation. Altogether, a more severe inflammatory reaction that is associated with the AA genotype could lead to autoimmune diseases and cancer and prevent infection, indicating the fragile balance between immunity and inflammation through IL-17A.

To date, no studies have reported a relationship between pain-related phenotypes and the rs2275913 SNP of the *IL-17A* gene or

IL-17A in humans. To clarify the association between IL-17A and somatic and neuropathic pain after orthognathic surgery in humans, we analyzed the association between the rs2275913 SNP of the *IL-17A* gene and perioperative analgesic use in patients who underwent cosmetic orthognathic surgery. The AA genotype of rs2275913 of the *IL-17A* gene was associated with higher perioperative opioid requirements, indicating that the AA genotype of this SNP may be related to the pain-related phenotype.

## 2 | MATERIALS AND METHODS

### 2.1 | Ethics statement

The study was conducted according to the principles of the Declaration of Helsinki and approved by the Institutional Review Boards of Tokyo Dental College (Tokyo, Japan) and Tokyo Institute of Psychiatry (currently Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan). Written informed consent was obtained from all of the patients or their parents if required.

### 2.2 | Patients

A total of 354 healthy patients (American Society of Anesthesiologists Physical Status I, 15–52 years old, 125 males and 229 females) who were scheduled to undergo cosmetic orthognathic surgery (mandibular sagittal split ramus osteotomy) for mandibular prognathism at Tokyo Dental College Suidoubashi Hospital completed the study. All of the subjects were Japanese. Patients with chronic pain who were taking pain medication and had experienced Raynaud's phenomenon were excluded.

### 2.3 | Preoperative cold pressor-induced pain test

The patients were premedicated with oral diazepam, 5 mg, and oral famotidine, 150 mg, 90 minutes before the induction of anesthesia. The patients had an intravenous (i.v.) line inserted in the forearm on their nondominant side. The temperature in the operating room was maintained at 26°C. The cold pressor-induced pain test was then performed before and 3 minutes after an i.v. bolus injection of fentanyl, 2 µg/kg, as previously described.<sup>21,22</sup> Crushed ice cubes and cold water were blended 15 minutes before the test in a 5-L isolated tank, and the mixture was stirred immediately before each test to ensure uniform temperature distribution (0°C) within the tank. The dominant hand was immersed up to the wrist. The patients were instructed to keep their hand calm in the ice-cold water and withdraw it as soon as they perceived any pain. All of the patients were tested by the same investigator. The baseline latency to pain perception, defined as the time of immersion of the hand in the ice water before the i.v. injection of fentanyl (PPLpre), was recorded. A cutoff point of 150 s was set to avoid tissue damage. The hand was warmed with a hair dryer as soon as it was withdrawn from the ice water until the sensation of cold was completely abolished.



The patients then received i.v. fentanyl, 2 µg/kg. Three minutes after the injection, the latency of pain perception of the dominant hand (PPLpost) was measured again. The difference between PPLpre and PPLpost (PPLpost-PPLpre) was defined as the preoperative analgesic effect.

## 2.4 | Anesthesia and surgery

General anesthesia was induced with a target-controlled infusion (TCI) of propofol using a TCI pump (TE-371, Terumo, Tokyo, Japan). Vecuronium, 0.1 mg/kg, was administered to facilitate nasotracheal intubation. After the induction of anesthesia, 10 mL of venous blood was sampled for the preparation of DNA specimens. General anesthesia was maintained with propofol at a target blood concentration of 4–6 µg/mL. Vecuronium was administered at a rate of 0.08 mg/kg/h. The lungs were ventilated with oxygen-enriched air. Local anesthetic block was performed on the right side of the surgical field with 8 mL of 2% lidocaine that contained epinephrine, 12.5 µg/mL, and right mandibular ramus osteotomy was performed. Local anesthetic block was then performed on the left side, and left mandibular ramus osteotomy was performed. The bilateral mandibular bone segments were fixed in appropriate positions. Whenever systolic blood pressure or heart rate exceeded +20% of the preinduction value during surgery, i.v. fentanyl, 1 µg/kg, was administered.

## 2.5 | Postoperative pain management

At the end of surgery, rectal diclofenac sodium, 50 mg, and i.v. dexamethasone, 8 mg, were administered at the request of surgeons to prevent postoperative orofacial edema/swelling. After emergence from anesthesia and tracheal extubation, droperidol, 1.25 mg, was administered i.v. to prevent nausea/vomiting, and i.v. patient-controlled analgesia (PCA) with a fentanyl-droperidol combination (2 mg fentanyl and 5 mg droperidol diluted in normal saline in a total volume of 50 mL) commenced using a CADD-Legacy PCA pump (Smiths Medical Japan, Tokyo, Japan). A bolus dose of fentanyl on demand and lockout time were set at 20 µg and 10 minutes, respectively. Continuous background infusion was not employed. Droperidol was coadministered with fentanyl to prevent nausea/vomiting because our preliminary study showed a high incidence (up to 30%) of nausea/vomiting with PCA fentanyl in young females. Patient-controlled analgesia was continued for 24 hours postoperatively. In the case of treatment-refractory adverse effects or inadequate analgesia, PCA was discontinued, and rectal diclofenac sodium, 50 mg, was prescribed as a rescue analgesic as required. The intensity of spontaneous pain was assessed at 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. Intraoperative fentanyl use, postoperative PCA fentanyl use during the first 24 hours postoperative period, and perioperative (ie, intraoperative + postoperative) fentanyl use were recorded. The doses of fentanyl that were administered intraoperatively and postoperatively were normalized to body weight.

## 2.6 | Genotyping

Genomic DNA was extracted from whole-blood samples using standard procedures. The extracted DNA was dissolved in TE buffer (10 mmol/L Tris-HCl and 1 mmol/L EDTA, pH 8.0). The DNA concentration was adjusted to 100 ng/µL for whole-genome genotyping using a NanoDrop ND-1000 Spectrophotometer (NanoDrop Technologies, Wilmington, DE, USA). Genotype data of the rs2275913 SNP were obtained from the results of whole-genome genotyping, which was performed using HumanOmniExpressExome-8 BeadChips and Infinium assay II with an iScan system (Illumina, San Diego, CA, USA) according to the manufacturer's instructions, as described in detail in a previous study.<sup>23</sup> The genotyping results for the rs2275913 SNP were qualified by a data-cleaning process using GenomeStudio with the Genotyping v3.3.7 module (Illumina). In the data-cleaning process, markers with a genotype call frequency of less than 0.95, "Cluster sep" (ie, an index of genotype cluster separation) of less than 0.1, or *P* values (*df* = 1) less than 0.001 in the Hardy-Weinberg equilibrium tests were excluded from the subsequent association study.

## 2.7 | Statistical analysis

The patients' demographic and clinical data are expressed as mean ± SD or median [interquartile ranges]. The statistical analysis was performed using SPSS 20.0.0 or 24.0.0.0 software (IBM, Tokyo, Japan). Because the clinically measured endpoints that were related to pain sensitivity (ie, PPLpre [s] and PPLpost-PPLpre [s]) and fentanyl analgesia (ie, total perioperative analgesic use and VAS scores at 24 hours postoperatively) were not normally distributed, nonparametric analyses (Mann-Whitney *U* test and Spearman's rank correlation test) were used to detect possible associations between the clinical and genomic parameters (eg, sex, age, and genotypes of the SNP) and clinical endpoints that were related to pain sensitivity and the analgesic effects of fentanyl. Although multiple factors other than the genotypes of the screened SNPs (eg, age and sex) may also affect fentanyl analgesia, thus suggesting the use of multivariate covariate analyses, the nonparametric distributions of most of our data precluded the application of such parametric techniques. The effects of sex and age on pain-related phenotypes were evaluated using nonparametric analyses in a previous study.<sup>24</sup> According to most previous reports of the rs2275913 SNP, a recessive model led to significant differences.<sup>9–13</sup> Therefore, we also adopted a recessive model (AA vs AG + GG) to divide the patients. When a significant association was found between a genotype and a clinical endpoint, factors other than genotype were compared between genotypes using unpaired *t* tests, Fisher's exact test, or the Mann-Whitney *U* test according to the types of data to evaluate whether the genotype groups were controlled for other factors that might affect pain sensitivity, fentanyl analgesia, or fentanyl requirements, including age, sex, the duration of surgery, and the duration of anesthesia. Values of *P* < .05 were considered statistically significant. The sample size of

**TABLE 1** Clinical data of patients who underwent cosmetic orthognathic surgery

Phenotype	rs2275913 SNP genotype			
	AA	AG	GG	AG + GG
Number of patients (males/females)	49 (14/35)	175 (64/111)	130 (47/83)	305 (111/194)
Age (y)	24.8 ± 6.7	26.3 ± 7.9	25.9 ± 7.6	26.1 ± 7.8
PPLpre (s)	13 [9, 23]	14 [9, 22]	15 [10, 24] <sup>a</sup>	14 [9, 23] <sup>b</sup>
PPLpost (s)	26 [17, 53]	26 [15, 49]	30 [18, 57] <sup>a</sup>	28 [16, 53] <sup>b</sup>
PPLpost-PPLpre (s)	11 [6.0, 33]	12 [3, 31]	12 [5, 36] <sup>a</sup>	12 [4, 35] <sup>b</sup>
Duration of anesthesia (min)	170 [160, 192]	174 [159, 193]	171 [157, 193]	173 [158, 193]
Duration of surgery (min)	103 [92, 125]	108 [95, 127]	104 [89, 120]	106 [92, 124]
Total propofol dose (mg/kg)	25.3 [22.0, 29.5]	26.3 [22.7, 29.8]	26.2 [22.6, 29.4]	26.2 [22.6, 30.0]
Preoperative fentanyl use (μg/kg)	2.0	2.0	2.0	2.0
Intraoperative fentanyl use (μg/kg)	5.3 [3.6, 6.5]	4.4 [3.4, 5.9]	4.0 [2.9, 5.1]	4.1 [3.2, 5.8]
24 h postoperative fentanyl use (μg/kg)	2.6 [1.8, 5.0]	2.2 [0.9, 4.5]	2.2 [1.2, 3.9]	2.2 [1.0, 4.1]
Perioperative fentanyl use (μg/kg)	8.2 [6.1, 10.3]	6.9 [5.2, 9.2]	6.6 [5.1, 8.5]	6.8 [5.1, 9.0]
Total perioperative analgesic use (μg/kg)	8.9 [7.1, 11.3]	8.0 [6.0, 10.2]	7.5 [5.9, 9.4]	7.6 [6.0, 10.0]
VAS pain score at 3 h (mm)	32.0 [14.0, 50.0]	25.0 [15.0, 50.0]	27.5 [15.3, 50.0]	26.0 [15.0, 50.0]
VAS pain score at 24 h (mm)	27.0 [10.0, 42.0]	25.0 [10.0, 40.0]	25.0 [8.0, 44.3]	25.0 [10.0, 42.0]

The data are expressed as numbers, mean ± SD (range), or median [interquartile range].

<sup>a</sup>n = 129 (male/female: 47/82).

<sup>b</sup>n = 304 (male/female: 111/193).

the present nonparametric data was higher than the estimated size that possesses statistical power (1 minus type II error probability) of 90% for Cohen's conventional "medium" effect size of 0.3. Power analyses were performed using G\*Power v.3.0.9.2.<sup>25</sup>

To explore the association between the rs2275913 SNP and pain-related phenotypes, the Mann-Whitney *U* test was performed. For this analysis, pain-related phenotypes and genotype data for the rs2275913 SNP were incorporated as dependent and independent variables, respectively. Values of *P* < .05 were considered statistically significant. The box and whisker plots were graphed using GraphPad Prism 7 software. To examine the linearity of opioid requirements that depended on the A allele of the rs2275913 SNP, linear regression analysis with an additive genetic model was performed. Prior to the analysis, the quantitative values of total perioperative analgesic use (μg/kg) were natural log-transformed for approximation to the normal distribution according to the following formula: Value for analysis = Ln (1 + postoperative analgesic requirement [μg/kg]).

### 3 | RESULTS

#### 3.1 | Patient characteristics

A total of 354 Japanese patients were included in the analysis. The patients' demographic and clinical data are shown in Table 1. A previous study of this same group of patients reported that sex was not significantly associated with the latency to pain perception before fentanyl administration in the cold pressor-induced pain test (PPLpre) or VAS 3 or 24 hours after surgery. The analgesic effect of fentanyl in the cold pressor-induced pain test (PPLpost-PPLpre) was

significantly greater in males than in females (*P* = .009), and total perioperative analgesic use was significantly less in males than in females (*P* < .001; Mann-Whitney *U* test).<sup>24</sup> The study also reported that age was not significantly associated with any of the clinical endpoints (Spearman's rank correlation test), and PPLpost-PPLpre was not associated with VAS pain scores at 24 hours.<sup>24</sup> The minor A allele frequency of the rs2275913 SNP of the *IL-17A* gene was 39% in the Japanese population in this study.

#### 3.2 | Statistical analysis

In this study, Pearson's chi-squared test or classic multidimensional scaling revealed no significant difference in sex or age among the subjects who carried different genotypes of the rs2275913 SNP (*P* > .05), indicating that the clinical outcomes among genotypes were not influenced by sex or age. The clinically measured endpoints that were related to pain sensitivity (ie, PPLpre and PPLpost-PPLpre) and analgesic effects (ie, total operative analgesic use and VAS pain scores at 24 hours) were unrelated to the rs2275913 SNP and were not normally distributed. Therefore, nonparametric analysis was used to detect possible associations between the rs2275913 SNP and clinical endpoints that were related to opioid requirements and VAS pain scores.

#### 3.3 | Effects of rs2275913 SNP on pain-related phenotypes

The Mann-Whitney *U* test revealed a significant difference in total perioperative analgesic use between the AA group and AG + GG

**TABLE 2** Association between pain phenotype and rs2275913 SNP (*P* value)

Pain phenotype	rs2275913 SNP genotype AA vs AG + GG		
	Total	Males	Females
PPLpre	0.799	0.251	0.378
PPLpost-PPLpre	0.909	0.296	0.656
Total perioperative analgesic use	0.009**	0.111	0.044*
VAS pain score at 24 h	0.993	0.508	0.691

PPL, latency to pain perception; VAS, visual analog scale.

\**P* < .05, \*\**P* < .01.

group of the rs2275913 SNP for males and females combined and for females alone (converted to fentanyl doses; males and females combined: *P* = .00901; females: *P* = .0443; Table 2), whereas the difference was not significant for males only (males: *P* = .111). As represented by box and whisker plots in Figure 1A, the AA group required more analgesics than the AG + GG group. Even when the samples were divided into 3 groups, the AA group required more analgesics than the AG and GG groups, based on median opioid requirements. Median opioid requirements linearly increased as the copy number of the minor A allele of the SNP increased (Figure 1B). To clearly demonstrate linearity, we adopted linear regression analysis. Linear regression analysis with an additive genetic model revealed a positive correlation between opioid requirements and the copy number of the A allele of the SNP in the combined group of males and females (*P* = .00776). Thus, for males and females combined, opioid requirements linearly increased as the copy number of the A allele of the SNP increased.

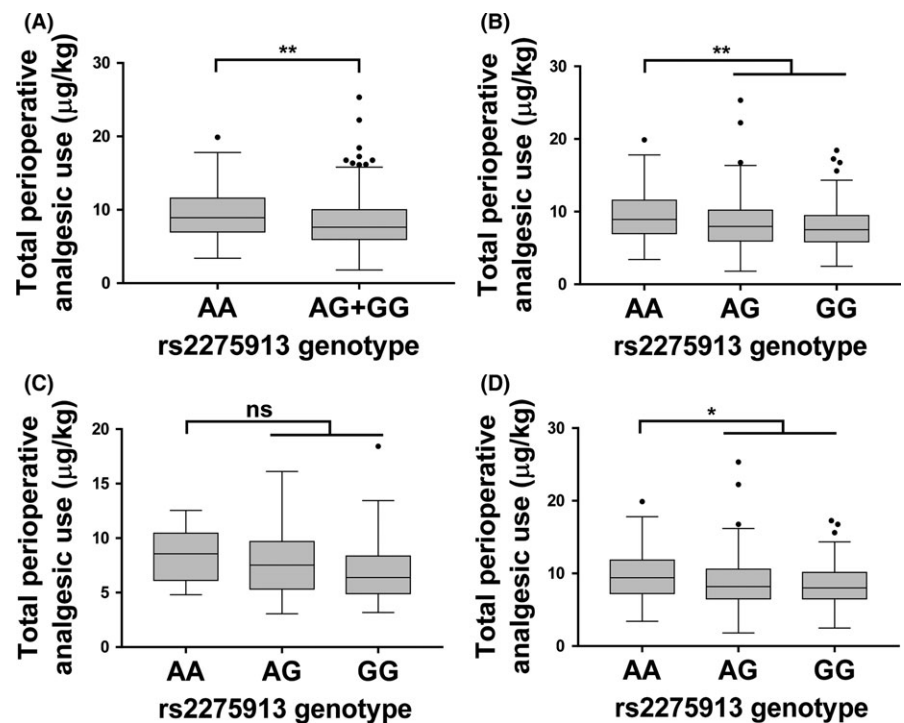
With regard to sex differences, the AA group required more analgesics than the AG + GG group for both males and females, although only females exhibited a statistically significant difference (Figure 1C, D). Median opioid requirements incrementally increased as the copy number of the A allele increased for both males and females (Figure 1C, D). The linear regression analysis that utilized an additive genetic model indicated that both males and females exhibited a trend toward a positive correlation between opioid requirements and the copy number of the A allele of the SNP, although this correlation was not statistically significant (males: *P* = .0939; females: *P* = .0503). Altogether, both males and females presented similar trends as males and females combined in the association between the A allele and opioid requirements.

The rs2275913 SNP was not significantly associated with PPLpre (males and females combined: *P* = .799; males: *P* = .251; females: *P* = .378; Table 2), PPLpost-PPLpre (males and females combined: *P* = .909; males: *P* = .296; females: *P* = .656; Table 2), or VAS pain scores at 24 hours (males and females combined: *P* = .993; males: *P* = .508; females: *P* = .691; Table 2).

## 4 | DISCUSSION

It has been reported that pain has an impact on reward/motivation circuits in humans.<sup>26</sup> Together with the fact that the activation of the reward system enhances innate and adaptive immunity in humans,<sup>27</sup> pain relates to immune system through reward system in humans. The proinflammatory cytokine IL-17A has been shown to be related to hypersensitivity after peripheral nerve injury,

**FIGURE 1** Associations between genotypes of the rs2275913 SNP and total perioperative analgesic use after cosmetic orthognathic surgery (*n* = 354). 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 highest and lowest values. The median is depicted by a horizontal solid line in the box. Outliers and extreme values are shown as circles and triangles, respectively. ns, not significant. \**P* < .05, \*\**P* < .01. A, The samples were divided into 2 groups (AA and AG + GG); B, The samples were divided into 3 groups (AA, AG, and GG); C, The male samples were divided into 3 groups; D, The female samples were divided into 3 groups







neuropathic pain, and neuroinflammation in rodents,<sup>5-7</sup> but no studies have reported the pain-related functions of IL-17A in humans. The present study examined whether the rs2275913 SNP of the *IL-17A* gene affects pain sensitivity and opioid requirements during and after orthognathic surgery. Our results showed that the AA genotype of the rs2275913 SNP of the *IL-17A* gene influenced the pain-related phenotype (ie, opioid requirements), likely through the greater expression of IL-17A. Overall, the present study showed that the IL-17A inflammation pathway may be related to pain in humans.

Our results suggest that the amount of perioperative opioid requirements for somatic or neuropathic pain that is caused by orthognathic surgery increases incrementally as the copy number of the A allele of the rs2275913 SNP increases for both males and females combined. The rs2275913 SNP is located in the promoter region of the *IL-17A* gene. The A allele of the rs2275913 SNP was reported to upregulate the expression of IL-17A in humans.<sup>8</sup> IL-17A upregulation by the A allele of the rs2275913 SNP appears to increase opioid requirements incrementally as the copy number of the A allele increases. Altogether, the IL-17A-related inflammation pathway appears to contribute to perioperative inflammation that leads to somatic or neuropathic pain in humans, depending on IL-17A expression.

With regard to the action of IL-17A on the opioid system, morphine was shown to inhibit early IL-17A induction after pathogenic infection, leading to a lower protective response and sustained inflammation in mice.<sup>28-31</sup> Morphine was also shown to reduce IL-17A secretion from cultured CD4+ T cells from peripheral blood samples from morphine- and cannabinoid-addicted humans.<sup>32</sup> On the other hand, morphine exposure for 3 months increased the functional activity of Th17 cells in rhesus macaques.<sup>33</sup> Furthermore, mechanical allodynia and thermal hyperalgesia in rats after exposure to the  $\mu$ -opioid receptor agonist remifentanil were accompanied by an increase in IL-17A/IL-17RA expression.<sup>34</sup> Based on these reports, one possibility is that opioids induce steady-state IL-17A expression in healthy humans, whereas decrease IL-17A induction after infection or reduce IL-17A secretion in morphine- and cannabinoid-addicted humans. However, no studies have investigated the ways in which opioids affect IL-17A.

The total perioperative analgesic use differed significantly between the AA group and AG + GG group of the rs2275913 SNP for males and females combined and for females alone (converted to fentanyl doses; males and females combined:  $P = .00901$ ; females:  $P = .0443$ ; Table 2), whereas the difference was not significant for males alone (males:  $P = .111$ ). Fukuda et al found that total perioperative analgesic use was significantly less in males than in females of the same samples ( $P < .001$ ; Mann-Whitney  $U$  test).<sup>24</sup> Based on these previous findings, the increase in opioid requirements in females in the present study may be at least partially attributable to sex-dependent opioid requirements. Consequently, although males did not present a significant difference, males and females combined presented the most significant difference, and

the amount of opioid requirements increased incrementally as the copy number of the A allele increased for males and females combined. These results suggest that the A allele of the rs2275913 SNP of the *IL-17A* gene activates the IL-17A inflammation pathway more robustly after surgery, regardless of sex, and such activation depends on the copy number of the A allele of the rs2275913 SNP.

## ACKNOWLEDGMENTS

We are grateful to the anesthesiologists and surgeons for collecting the clinical data. This work was supported by grants from MEXT KAKENHI (no. 22790518, 23390377, 24659549, 24790544, 25116532, 26293347, 26860360, 15H01303, 16H06276, 16K15565, 17H04324, 17K09052, and 17K08970), Ministry of Health, Labour and Welfare (MHLW) of Japan (no. H21-3jigan-ippan-011, H22-lyaku-015, H25-lyaku-020, H26-Kakushintekigan-ippan-060, and 14524680), Japan Agency for Medical Research and Development (AMED; no. JP17mk0101076, JP17ek0610011, and JP17dk0307071), Smoking Research Foundation (Tokyo, Japan), and Astellas Foundation for Research on Metabolic Disorders (Tokyo, Japan).

## CONFLICT OF INTEREST

KI received support from Eisai for a project unrelated to this research and speaker's fees from Taisho Pharmaceutical Co., Ltd., Eisai, Daiichi-Sankyo, Inc., Sumitomo Dainippon Pharma, and Japan Tobacco, Inc.

## DATA REPOSITORY

Raw data are provided as Table S1.

## APPROVAL OF THE RESEARCH PROTOCOL BY AN INSTITUTIONAL REVIEWER BOARD

The study was conducted according to the principles of the Declaration of Helsinki and approved by the Institutional Review Boards of Tokyo Dental College (Tokyo, Japan) and Tokyo Institute of Psychiatry (currently Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan).

## INFORMED CONSENT

Written informed consent was obtained from all of the patients or their parents if required.

## REGISTRY AND THE REGISTRATION NO. OF THE STUDY/TRIAL

No. 086 for Tokyo Dental College, No. 15-6 for Tokyo Metropolitan Institute of Medical Science.

## ANIMAL STUDIES

n/a.

## AUTHOR CONTRIBUTIONS

SO, DN, and KI conceived and designed the experiments. JH and DN performed the experiments. SO, DN, KN, and YE analyzed the data. KT and KF contributed human samples. SO, DN, and KI wrote the manuscript.

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#### SUPPORTING INFORMATION

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

**How to cite this article:** Ohka S, Nishizawa D, Hasegawa J, et al. Association between rs2275913 single-nucleotide polymorphism of the *interleukin-17A* gene and perioperative analgesic use in cosmetic orthognathic surgery.

*Neuropsychopharmacol Rep*. 2018;38:67–74. <https://doi.org/10.1002/npr2.12010>