

Original Article



Associations between HLA-A, -B, and -C alleles and iodinated contrast media-induced hypersensitivity in Koreans

Eun-Young Kim ^{1,2}, Seok Jin Choi ³, Jong-Lyul Ghim ^{1,2}, Mi-Yeong Kim ⁴, Jung Eun Seol ⁵, Minkyung Oh ², Chan Sun Park ⁶, and Jae-Gook Shin ^{1,2,*}

¹Department of Clinical Pharmacology, Inje University Busan Paik Hospital, Busan 47392, Korea

²Department of Pharmacology and Pharmacogenomics Research Center, Inje University College of Medicine, Busan 47392, Korea

³Department of Radiology, Inje University Busan Paik Hospital, Busan 47392, Korea

⁴Department of Internal Medicine, Inje University Busan Paik Hospital, Busan 47392, Korea

⁵Department of Dermatology, Inje University Busan Paik Hospital, Busan 47392, Korea

⁶Department of Internal Medicine, Inje University Haeundae Paik Hospital, Busan 48108, Korea



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*Correspondence to

Jae-Gook Shin

Department of Clinical Pharmacology, Inje University Busan Paik Hospital, and Department of Pharmacology and Pharmacogenomics Research Center, Inje University College of Medicine, 75 Bokji-ro, Busanjin-gu, Busan 47392, Korea.
E-mail: phshinjg@gmail.com

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ORCID iDs

Eun-Young Kim

<https://orcid.org/0000-0003-0125-2173>

Seok Jin Choi

<https://orcid.org/0000-0002-2688-4006>

Jong-Lyul Ghim

<https://orcid.org/0000-0002-6137-786X>

Mi-Yeong Kim

<https://orcid.org/0000-0002-2640-6258>

Jung Eun Seol

<https://orcid.org/0000-0002-3029-9635>

Minkyung Oh

<https://orcid.org/0000-0001-7584-5436>

Chan Sun Park

<https://orcid.org/0000-0003-0113-8354>

Jae-Gook Shin

<https://orcid.org/0000-0002-5821-850X>

ABSTRACT

A common cause of drug hypersensitivity reactions is iodinated contrast media (ICM). ICM-induced hypersensitivity had been considered to be a non-immunological reaction, but evidence for an immunological mechanism has increased recently. Thus, we evaluated whether HLA-A, -B, and -C alleles were associated with ICM-induced hypersensitivity. In total, 126 patients who underwent contrast-enhanced computed tomography studies through outpatient clinics at a tertiary referral hospital between 2008 and 2012 were assessed. Sixty-one patients experienced ICM-induced hypersensitivity and the remainder, 65, were ICM-tolerant patients (control). ICM-induced hypersensitivity patients showed 51 with immediate, 7 with non-immediate, 3 with both or mixed type. HLA-A, -B, and -C genotyping was performed using a PCR sequence-based typing method. Four kinds of ICM were used: iopromide, iohexol, iobitridol, and iodixanol. The most used ICM among the hypersensitivity patients was iopromide. Significant difference in the frequency of *HLA-B*58:01* (odds ratios [OR], 3.90; $p = 0.0200$, 95% confidence interval [CI], 1.16–13.07) was observed between ICM-induced immediate hypersensitivity and control. There were statistically significant differences in the frequencies of the *HLA-B*38:02* (OR, 10.24; $p = 0.0145$; 95% CI, 1.09–96.14) and *HLA-B*58:01* (OR, 3.98; $p = 0.0348$; 95% CI, 1.03–15.39) between iopromide-induced immediate hypersensitivity and control. The mechanism of ICM-induced hypersensitivity remains unknown, but this study showed associations, although weak, with *HLA-B*58:01* alleles for ICM-induced immediate hypersensitivity and *HLA-B*38:02* and *HLA-B*58:01* for iopromide-induced immediate hypersensitivity as risk predictors. Further studies are needed to validate the associations in larger samples and to identify the functional mechanism behind these results.

Keywords: Iodinated Contrast Media; Immediate Hypersensitivity; Non-immediate Hypersensitivity; Korean; HLA Class I

INTRODUCTION

Iodinated contrast media (ICM) are important agents for diagnostic purposes in the field of radiology, but they are known to be a common cause of drug hypersensitivity reactions

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[1]. The occurrence of ICM-induced hypersensitivity has decreased since non-ionic ICM were introduced to replace ionic ICM [2]. The prevalence of hypersensitivity to ICM was reported to be 1.1% in Koreans [3] in our previous retrospective study. Although the rate is not high, ICM are used widely worldwide, which can result in a large number of ICM-induced hypersensitivity cases. ICM-induced hypersensitivity is generally classified into immediate (acute) and non-immediate (delayed) reactions. The former occurs within 1 hour and the latter occurs from 1 hour to 7 days after ICM exposure usually. ICM-induced hypersensitivity reactions had been considered to be non-immunological reactions, caused by chemical and molecular toxicity, overdose, and the physiological properties of ICM [4-6], but evidence for an immunological mechanism has increased recently. Trcka et al. [7] reported that about 4% of 96 patients with anaphylactic (immediate) symptoms showed positive skin and basophil activation tests, suggesting an immunoglobulin E (IgE)-mediated allergy. T-cell mediated non-immediate skin reactions after ICM exposure were also reported as evidence of allergic reactions [8,9]. Immediate and non-immediate hypersensitivity after ICM exposure has been reported to be immune-mediated reactions, based on positive skin and *in vitro* tests in patients and on cell-based experiments [7-10].

HLA type has been mainly studied as a risk factor in non-immediate hypersensitivity reactions [11,12]. HLA is a genetic factor that synthesizes major histocompatibility complex (MHC). The MHC molecule on the antigen-presenting cell presents the antigen to the T cell with an autologous peptide after processing the protein of drug metabolites. Various factors such as antigen structure, T cell receptor (TCR), and secondary signals affect this binding [13,14]. However, studies on HLA, which are relatively well-known and easy to test, have been mostly conducted. Recently, a study has been reported that HLA can be a risk factor even in immediate hypersensitivity reaction, anaphylaxis [15].

Currently, the mechanism of ICM-induced hypersensitivity is not fully understood, and studies of associations between hypersensitivity and HLA alleles may contribute to the identification of this mechanism. Thus, in this study, we evaluated the associations between HLA-A, -B, and -C alleles and ICM-induced hypersensitivity in immediate and non-immediate reactions.

METHODS

Subjects and samples

The subjects were 126 patients among total of 266 patients who underwent contrast-enhanced computed tomography studies through outpatient clinics of a tertiary referral hospital, Inje University Busan Paik Hospital, between 2008 and 2012 (**Figure 1**). Ninety-four patients were recruited prospectively, before ICM administration, or immediately after hypersensitivity reactions, and the rest were retrospectively recruited. Sixty-one subjects had hypersensitivity reactions to ICM (case) and the remainder (65) did not (control). Patients with only adverse reactions considered to be physiological responses such as nausea and chilling sensation were not included in both the case and control groups. All control were recruited before intravenous administration of ICM and 29 case patients were recruited before intravenous administration of ICM (8 cases) or immediately after hypersensitivity reactions. Data regarding hypersensitivity reactions were collected prospectively from November 2010 to August 2012. Non-immediate reactions were checked by calling subjects 48 hours after ICM administration. The remaining 32 cases were recruited retrospectively, after searching for patients with adverse reactions noted on electronic medical records

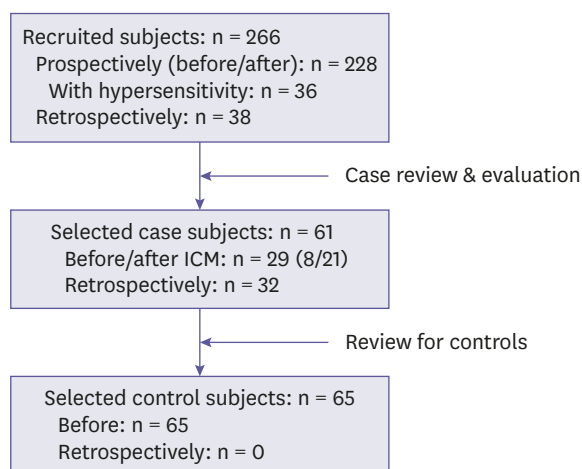


Figure 1. The process of subject selection for ICM-induced hypersensitivity (case) and ICM-tolerant (control) patients. All case patients were recruited before ICM administration. Case patients were recruited prospectively, before ICM administration (8) and immediate after hypersensitivity reactions at the site (21), and retrospectively after searching for patients with adverse reactions noted on electronic medical records (32). All case and control patients were evaluated and selected by specialists. ICM, iodinate contrast media.

(EMRs) from 2008 to 2012. Blood samples for genotype analyses were collected with EDTA tubes, except for seven retrospectively recruited patients where dried blood spot papers were used. The data collected from EMRs and history taking included age, sex, diagnosis (cancer vs. no cancer), previous exposure to ICM, prior experiences of ICM-induced hypersensitivity, oral premedication use before ICM exposure, ICM administration time, hypersensitivity signs/symptoms, reaction onset time, and patient management after the reaction. The severity of hypersensitivity was classified as mild, moderate, or severe using the grading system in the ACR Manual on Contrast Media (ver. 8, 2012) [16].

All subjects gave informed consent to participate in the study. The study was approved by the institutional review board of Busan Paik Hospital, Busan, Republic of Korea (IRB No. 10-122).

Sequence-based typing of HLA-A, -B, and -C

Genomic DNA was extracted from peripheral blood using the QIAamp Blood Mini Kit (QIAGEN, Hilden, Germany) or dried blood spots on paper (FTA Mini Card; Whatman, Florham Park, NJ, USA). Sequence-based typing of HLA-A, -B, and -C was performed with pairs of amplification and sequencing primers, as described previously [17]. PCR was carried out in a 30- μ L reaction volume that consisted of 100 ng genomic DNA, 1 \times PCR buffer, 0.2 mmol/L dNTPs, 0.4 mmol/L primers, 2.5 mmol/L MgCl₂, 1 \times Band Doctor, and 1 U EF Taq polymerase (Solgent, Deajeon, Korea). PCR was performed using a 9700 Thermal Cycler (Applied Biosystems, Foster City, CA, USA) with the following conditions: initial denaturation at 95°C for 2 min, followed by 30 cycles of 95°C for 30 s, 62–67°C for 40 s, 72°C for 1 min 40 s, and a final elongation step at 72°C for 5 min. The entire PCR product was sequenced directly using a 3130 DNA Sequencer (Applied Biosystems). HLA-A, -B, and -C genotypes were determined by analysis of sequencing data using the SBT Engine software (ver. 2.20; GenDx, Utrecht, the Netherlands).

Statistical analysis

HLA-A, -B, and -C allele frequencies were compared between patients with ICM-induced hypersensitivity and control patients using χ^2 and Fisher's exact tests. The case patients

were categorized 3 groups; i) immediate and ii) non-immediate after using any ICM, and iii) induced by the most commonly used ICM among case patients. The p -values < 0.05 were considered to indicate statistical significance. Odds ratios (ORs) and 95% confidence intervals were calculated, with Haldane's modification applied when a zero-count field was encountered. All statistical analyses were performed using the SAS software (ver. 9.4; SAS Institute, Cary, NC, USA).

RESULTS

Four kinds of ICM were used: the non-ionic monomers iopromide, iohexol, and iobitridol, and the non-ionic dimer iodixanol. The characteristics of patients with ICM-induced hypersensitivity and ICM-tolerant patients using above four kind of ICM, are shown in **Table 1**. The sample contained more female than male patients, and the average age of all patients was 54.9 years. The numbers of immediate, non-immediate cases, and controls with two or more ICM exposures were 35, 6, and 44, respectively. Twenty-five patients experienced hypersensitivity at their first ICM exposures, and six of these patients had two or more hypersensitivity events. The average number of reactions was 1.4 (range, 1–4); 20 patients experienced two or more hypersensitivity reactions. A total of 85 hypersensitivity events occurred in the case group and 75 events were immediate and 9 were non-immediate. One case was a mixed type, immediate reaction followed by non-immediate reaction. Among 61 patients with ICM-induced hypersensitivity, 51 had immediate reactions, 7 had non-immediate reactions, 2 had both, and one had a mixed reaction. Iopromide was the most common ICM, associated with 85 events, which accounted for 41.2% of the total. Iohexol was associated with 28.2% of events, iobitridol with 21.2%, and iodixanol was associated with 8.2% of events (**Table 1**). The ICM used was unknown in one retrospective case. Twenty-nine patients experienced immediate hypersensitivity after administration of iopromide. The most common symptom in both types of hypersensitivity was a skin reaction, such as urticaria and flushing. Most patients with hypersensitivity had skin reactions, with or without other symptoms. The other symptoms were gastrointestinal symptoms, such as nausea, cardiovascular symptoms, including lowered blood pressure and chest discomfort, respiratory symptoms, like dyspnea

Table 1. Characteristics of patients with ICM-induced hypersensitivity (all cases, immediate, non-immediate, both, and mixed) and ICM tolerance (control)

Variables	Cases (n = 61)	Immediate (n = 54)	Non-immediate (n = 10)	Both*† (n = 2)	Mixed†‡ (n = 1)	Control (n = 65)
No. of events	85	76	10	6	2	-
Age (yr)						
Mean \pm SD (range)	55.6 \pm 12.4	54.8 \pm 12.5 (29–78)	55.9 \pm 15.8 (31–77)	46.5 \pm 21.9 (31–62)	31	54.2 \pm 12.2 (26–79)
Sex						
Male, no. (%)	24 (39.3)	23 (42.6)	2 (20.0)	1 (50.0)	-	27 (41.5)
Female, no. (%)	37 (60.7)	31 (57.4)	8 (80.0)	1 (50.0)	1	38 (58.5)
No. of ICM exposures						
Mean \pm SD, range	5.1 \pm 5.2 (1–21)	5.2 \pm 5.4 (1–21)	4.7 \pm 4.5 (1–13)	7.5 \pm 7.8 (2–13)	1	5.6 \pm 5.7 (1–26)
No. of patients with cancer	35	30	6	1	-	38
No. of patients with ≥ 2 events	18	18	2	2	1	-
No. of ICM use (%)						
Iopromide	35 (41.2)	33 (44.0)	2 (20.0)	3 (50.0)	1 (100)	12 (18.5)
Iohexol	24 (28.2)	20 (26.7)	4 (40.0)	1 (16.7)	-	39 (60.0)
Iobitridol	18 (21.2)	16 (21.3)	2 (20.0)	1 (16.7)	-	12 (18.5)
Iodixanol	7 (8.2)	5 (6.7)	2 (20.0)	1 (16.7)	-	2 (3.1)
Unknown	1 (1.2)	1 (1.3)	-	-	-	-

ICM, iodinated contrast media; SD, standard deviation; No., number.

*Patients with both immediate and non-immediate reactions to each ICM exposure; †Patient with immediate reaction followed by non-immediate reaction in one ICM exposure; ‡The events were added to the numbers of cases, immediate, and non-immediate patients.

and rhinorrhea, and neurological symptoms, such as dizziness and loss of consciousness. The severity was evaluated according to the ACR criteria [16], most cases were mild or moderate and only one case was severe.

The frequencies of the *HLA-B*46:01* and *-B*58:01* alleles were higher, and that of *-C*06:02* was lower, in patients with ICM-induced immediate hypersensitivity using at least one of the four ICMs compared with control patients (**Table 2**). These frequency patterns were similar to those in the general Korean population. The frequencies in the general Korean population were 5.06% for *HLA-B*46:01*, 6.77% for *-B*58:01*, and 6.36% for *-C*06:02* [18]. The differences in these three alleles between patients with ICM-induced immediate hypersensitivity and control patients were significant. The frequencies of the *HLA-B*46:01*, *-B*58:01*, and *-C*06:02* alleles were associated with ICM-induced immediate hypersensitivity compared with controls, with ORs of 4.69 ($P = 0.0423$), 3.9 ($P = 0.0200$), and 0.08 ($P = 0.0220$), respectively. However, only *HLA-B*58:01* allele did not include 1 in 95% confidential interval (CI).

The frequency of the *HLA-B*15:11* allele was higher in patients with ICM-induced non-immediate hypersensitivity using at least one of the four ICMs compared with control patients (**Table 2**). The frequency of the allele in the general Korean population was 1.55% [18]. The frequency of the *HLA-B*15:11* allele was associated with ICM-induced non-immediate hypersensitivity compared with control (OR = 38.53; $P = 0.0003$; 95% CI, 0.22–110.52), but it was not statistically significant.

The frequencies of the *HLA-B*38:02* and *-B*58:01* alleles were higher in patients with immediate hypersensitivity after administration of iopromide compared with control patients (**Table 2**). The frequency of *HLA-B*38:02* allele in the general Korean population was 0.82% [18]. The frequencies of the *HLA-B*38:02* and *-B*58:01* alleles were associated significantly with immediate hypersensitivity after exposure to iopromide compared with control with ORs of 10.24 ($P = 0.0145$) and 3.98 ($P = 0.0348$), respectively. The control included patients exposed to all ICMs, not those exposed to the only iopromide.

The frequencies of HLA-A, -B, and -C alleles in all patients with ICM-induced hypersensitivity and ICM tolerance and the allele frequency of Korean population [18] are provided in **Table 3**. Sixteen patients each in the case and control groups were *HLA-B*58:01*-positive and carried *-A*33:03* and *-C*03:02*, except for one patient in the case group. The one severe case, based on ACR criteria, had no risk alleles. The patient showed loss of consciousness for a few seconds and urticaria with angioedema, nausea, flushing, sweating, and edema in the extremities.

Table 2. HLA-A, -B, and -C alleles associated with ICM-induced hypersensitivity in immediate, non-immediate, and immediate after iopromide administration

Allele	Frequency (%)		<i>p</i> -value	Odds ratio	95% CI
	Case* (n = 61)	Control† (n = 65)			
Immediate (n = 54)					
<i>B*46:01</i>	7 (12.96)	2 (3.08)	0.0423	4.69	0.93–23.62
<i>B*58:01</i>	11 (20.37)	4 (6.15)	0.0200	3.90	1.16–13.07
<i>C*06:02</i>	0 (0.00)	6 (9.23)	0.0220	0.08	0.02–6.20
Non-immediate (n = 10)					
<i>B*15:11</i>	2 (20.00)	0 (0.00)	0.0003	38.53	0.22–110.52
Immediate after iopromide (n = 29)					
<i>B*38:02</i>	4 (13.79)	1 (1.54)	0.0145	10.24	1.09–96.14
<i>B*58:01</i>	6 (20.69)	4 (6.15)	0.0348	3.98	1.03–15.39

ICM, iodinated contrast media; CI, confidence interval.

*ICM-induced hypersensitivity; †ICM tolerance.

Table 3. Frequencies of HLA alleles in ICM-induced hypersensitivity (case, n = 61) and ICM-tolerant (control, n = 65) patients and AF of Korean population (n = 613) [18]

Allele	Frequency (%)		Korean AF (%)	Allele	Frequency (%)		Korean AF (%)	Allele	Frequency (%)		Korean AF (%)
	Case	Control			Case	Control			Case	Control	
A*01:01	0 (0.00)	1 (1.54)	1.88	B*13:02	0 (0.00)	4 (6.15)	4.16	B*56:01	1 (1.64)	1 (1.54)	0.08
A*02:01	17 (27.87)	17 (26.15)	17.62	B*14:01	1 (1.64)	2 (3.08)	1.96	B*58:01	12 (19.67)	4 (6.15)	6.77
A*02:03	3 (4.92)	2 (3.08)	0.73	B*15:01	12 (19.67)	10 (15.38)	8.73	B*59:01	0 (0.00)	4 (6.15)	1.71
A*02:06	8 (13.11)	10 (15.38)	9.46	B*15:11	3 (4.92)	0 (0.00)	1.55	B*67:01	1 (1.64)	0 (0.00)	0.90
A*02:07	3 (4.92)	4 (6.15)	3.51	B*27:05	3 (4.92)	1 (1.54)	3.10	C*01:02	20 (32.79)	19 (29.23)	17.81
A*03:01	3 (4.92)	1 (1.54)	1.55	B*35:01	7 (11.48)	11 (16.92)	6.12	C*01:03	0 (0.00)	1 (1.54)	0.08
A*03:02	1 (1.64)	1 (1.54)	0.08	B*37:01	0 (0.00)	2 (3.08)	2.12	C*03:02	11 (18.03)	5 (7.69)	7.42
A*11:01	15 (24.59)	7 (10.77)	7.91	B*38:02	5 (8.20)	1 (1.54)	0.82	C*03:03	6 (9.84)	16 (24.62)	11.83
A*11:02	0 (0.00)	1 (1.54)	0.49	B*39:01	2 (3.28)	2 (3.08)	0.90	C*03:04	8 (13.11)	15 (23.08)	8.97
A*24:02	24 (39.34)	34 (52.31)	22.68	B*40:01	2 (3.28)	7 (10.77)	3.83	C*04:01	2 (3.28)	8 (12.31)	4.89
A*26:01	1 (1.64)	7 (10.77)	2.61	B*40:02	3 (4.92)	5 (7.69)	4.24	C*05:01	1 (1.64)	2 (3.08)	1.47
A*26:02	2 (3.28)	1 (1.54)	2.28	B*40:03	2 (3.28)	1 (1.54)	0.57	C*06:02	0 (0.00)	6 (9.23)	6.36
A*29:01	0 (0.00)	2 (3.08)	0.33	B*40:06	5 (8.20)	11 (16.92)	3.59	C*07:01	2 (3.28)	4 (6.15)	0.16
A*30:01	0 (0.00)	4 (6.15)	3.92	B*44:02	1 (1.64)	2 (3.08)	1.47	C*07:02	6 (9.84)	13 (20.00)	7.26
A*30:04	2 (3.28)	2 (3.08)	2.12	B*44:03	14 (22.95)	11 (16.92)	8.16	C*08:01	1 (1.64)	10 (15.38)	6.93
A*31:01	5 (8.20)	4 (6.15)	4.57	B*46:01	7 (11.48)	2 (3.08)	5.06	C*08:02	0 (0.00)	2 (3.08)	1.96
A*32:01	0 (0.00)	1 (1.54)	0.57	B*48:01	1 (1.64)	4 (6.15)	3.91	C*12:02	2 (3.28)	4 (6.15)	3.10
A*33:03	27 (44.26)	21 (32.31)	16.07	B*51:01	15 (24.59)	8 (12.31)	9.54	C*14:02	2 (3.28)	7 (10.77)	7.99
B*07:02	7 (11.48)	6 (9.23)	3.10	B*52:01	3 (4.92)	5 (7.69)	2.85	C*14:03	0 (0.00)	7 (10.77)	5.14
B*07:05	0 (0.00)	2 (3.08)	0.41	B*54:01	7 (11.48)	9 (13.85)	5.71	C*15:02	0 (0.00)	2 (3.08)	2.20
B*08:01	1 (1.64)	1 (1.54)	0.33	B*55:02	0 (0.00)	4 (6.15)	1.31	C*15:05	0 (0.00)	2 (3.08)	0.41
B*13:01	2 (3.28)	4 (6.15)	2.28	B*55:07	1 (1.64)	0 (0.00)	0.08				

ICM, iodinated contrast media; AF, allele frequency.

DISCUSSION

ICM-induced hypersensitivity remains a concern in practice because of the common use of ICM worldwide and the possible occurrence of severe or even fatal hypersensitivity reactions, although these are rare [19,20]. This hypersensitivity had been considered to be a non-immunological reaction [4-6], but allergic, immediate (acute) and non-immediate (delayed), reactions have been reported [7-10]. Thus, in this study we evaluated associations between HLA-A, -B, and -C genotypes and susceptibility to ICM-induced hypersensitivity; immediate and non-immediate of patients using at least one of the four ICMs, iopromide, iohexol, iobitridol, and iodixanol, and immediate reaction after administration of iopromide which was most commonly used ICM in hypersensitivity patients. Provocation tests such as skin prick, intradermal, and patch test are recommended for the diagnosis of ICM hypersensitivity in some patients who were suspected IgE or T-cell mediated reaction [21]. However, these limited tests are not for prevention but for the evaluation of causative agents and mechanisms. Genetic biomarker test is not only easier and more convenient but may also be used as a predictive marker to prevent the reaction. In this study we identified weak associations between HLA class I alleles and ICM-induced hypersensitivity in patients with immediate reactions and iopromide-induced immediate reactions as a subgroup of immediate cases, but not in a patient with non-immediate reactions. The association showed that *HLA-B*58:01* was a risk factor in the immediate hypersensitivity. It also showed that *HLA-B*38:02* and *-B*58:01* were risk factors in iopromide-induced immediate hypersensitivity. *HLA-B*58:01* was a risk factor of both ICM-induced in at least one of four, iopromide, iohexol, iobitridol, and iodixanol, and iopromide-induced immediate hypersensitivity reactions. The risk factors were HLA-B alleles. A recent study has been reported that HLA can be a risk factor even in immediate hypersensitivity reactions [15]. This study analyzed only anaphylaxis cases, but we included all subjects who experienced immediate and non-immediate reactions regardless of moderate severity. Thus there were no overlapped results as risk factors.

It was reported that *HLA-B*46:01* and *HLA-B*58:01* as protective factors and *HLA-B*15:11* as a risk factor for carbamazepine-induced SJS/TEN in the Asian population [22]. *HLA-B*58:01* is also a well-known risk factor of allopurinol-induced severe cutaneous adverse reactions in populations of various ethnicities, especially Asians [12]. The effect of HLA on the hypersensitivity reaction mechanism may differ depending on the type of drug or the difference in the distribution of HLA according to ethnicity. Each HLA allele would synthesize its own structure of MHC molecule. Depending on its final shape with drug antigen and a self-peptide, it may have a positive or negative effect on recognizing binding structure by TCR. The hypothesis that a specific HLA can play an opposite role in recognizing different drugs is sufficiently understandable [23]. A risk factor for iopromide-induced hypersensitivity, *HLA-B*38:02* was reported as a risk factor for an oxcarbazepine-induced maculopapular eruption in the Chinese population [24]. Fifteen of 16 patients with *HLA-B*58:01* also carried *HLA-A*33:03* and *HLA-C*03:02*, which could be explained as linkage disequilibrium, showing 6.77% haplotype frequency for *HLA-B*58:01* and *-C*03:02*, and 3.34% haplotype frequency for *HLA-A*33:03*, *-B*58:01*, *-C*03:02*, *-DRB1*13:02*, and *-DQB1*06:09* among Koreans [18]. Patients in the hypersensitivity group with *HLA-B*58:01* could carry the HLA class II genes *-DRB1*13:02* and *-DQB1*06:09*, which are possibly associated with risk or an additive effect, but we did not determine HLA class II genotypes in this study.

Most patients with previous experiences of ICM-induced hypersensitivity were pretreated with anti-histamines, systemic steroids, or systemic glucocorticoid and showed no adverse reaction or less severe reactions than with prior ICM use. Thus, we cannot say that patients who did not experience an event after a first hypersensitivity reaction were not at risk at that time, including the risk of genetic effects.

In our previous retrospective study [3], we identified cancer as a risk factor for ICM-induced hypersensitivity, which was explained partly by frequent contrast media exposure for follow-up studies [3]. The proportions of cancer patients in immediate, non-immediate, and control were similar (Table 1). In this study, 25 of 61 patients with ICM-induced hypersensitivity experienced reactions on first ICM exposure. Reports have described the detection of ICM-specific IgE antibodies and positivity on basophil activation tests [7] in patients who showed immediate hypersensitivity at first contact. They discussed whether the reaction after first exposure was immunogenic, but suggested the possibility of silent sensitization due to cross-reactivity with an unknown molecule in immediate and non-immediate reactions [10,25]. An advantage of this study was that patients in the control group were recruited prospectively, and the possibility of a non-immediate reaction in them was eliminated almost completely.

This study has several limitations and weaknesses, including the small sample; insufficient information on symptoms, including severity and onset time, in the retrospectively recruited cases; and the omission of skin and *in vitro* tests to determine whether the reactions were IgE or T cell mediated. However, the skin and *in vitro* tests are not perfect methods with 100% sensitivity and specificity, so there is a limitation that negative results cannot be said not to be IgE or T cell mediated response. Therefore, based on patients' history and symptoms, the case patients were selected for ICM-induced hypersensitivity and statistically significant factors were found. In this study, data analysis based on ICM type was performed only in iopromide administration cases, which was the most common cause of hypersensitivity in this study. For the analysis, the control included patients exposed to all ICMs, not only iopromide. However, cross-reactivity at the T cell level among the ICM may occur [26,27] and the similarity of chemical structures among various ICM may also result in the potential

for cross-reactivity [27]. This study also revealed that only two of 18 patients with ≥ 2 events occurred after using the same ICMs. Non-immediate reactions have been reported at the level of 1–3% with monitoring for 7 days after ICM exposure [28–30], but we did not monitor prospectively recruited subjects for 7 days. In addition, we genotyped only HLA class I, comprised of HLA-A, -B, and -C, and not HLA class II, which presents a limitation when interpreting the results.

In conclusion, we evaluated the associations between ICM-induced hypersensitivity and HLA class I alleles to assess the possibility that ICM-induced hypersensitivity is an immune-mediated reaction and found weak associations. The mechanism of the hypersensitivity remains unclear, but this study showed an association, although modest, with *HLA-B*58:01* as a risk factor in patients with mild to moderate ICM-induced immediate hypersensitivity. It also revealed risk factors, *HLA-B*38:02* and *-B*58:01* for a subgroup, iopromide-induced immediate hypersensitivity. There was no significant association between ICM-induced non-immediate hypersensitivity and HLA Class I alleles. We did not identify. Further studies are needed to validate these associations in larger numbers of cases and to identify the functional mechanism behind the results. Although the mechanism of the associations between the HLA alleles and hypersensitivity was not revealed, these results may contribute in part to determining the cause of ICM-induced hypersensitivity.

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REFERENCES

1. Heinzerling LM, Tomsitz D, Anliker MD. Is drug allergy less prevalent than previously assumed? A 5-year analysis. *Br J Dermatol* 2012;166:107-114.
[PUBMED](#) | [CROSSREF](#)
2. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. *Radiology* 1990;175:621-628.
[PUBMED](#) | [CROSSREF](#)
3. Kim HH, Choi JY, Oh MK, Kim EY, Ghim JL, Choi SJ, et al. Retrospective analysis of adverse reactions to iodinated contrast media in Korean. *J Korean Soc Clin Pharmacol Ther* 2012;20:165-174.
[CROSSREF](#)
4. Yamaguchi K, Katayama H, Kozuka T, Takashima T, Matsuura K. Pretesting as a predictor of severe adverse reactions to contrast media. *Invest Radiol* 1990;25 Suppl 1:S22-S23.
[PUBMED](#) | [CROSSREF](#)
5. Katayama H. The contrast media controversy: implications of a landmark safety study. *Adm Radiol* 1990;9:20-22.
[PUBMED](#)
6. Katayama H. Adverse reactions to contrast media. What are the risk factors? *Invest Radiol* 1990;25 Suppl 1:S16-S17.
[PUBMED](#) | [CROSSREF](#)
7. Trcka J, Schmidt C, Seitz CS, Bröcker EB, Gross GE, Trautmann A. Anaphylaxis to iodinated contrast material: nonallergic hypersensitivity or IgE-mediated allergy? *AJR Am J Roentgenol* 2008;190:666-670.
[PUBMED](#) | [CROSSREF](#)
8. Antunez C, Barbaud A, Gomez E, Audonnet S, Lopez S, Guéant-Rodriguez RM, et al. Recognition of iodixanol by dendritic cells increases the cellular response in delayed allergic reactions to contrast media. *Clin Exp Allergy* 2011;41:657-664.
[PUBMED](#) | [CROSSREF](#)

9. Kanny G, Pichler W, Morisset M, Franck P, Marie B, Kohler C, et al. T cell-mediated reactions to iodinated contrast media: evaluation by skin and lymphocyte activation tests. *J Allergy Clin Immunol* 2005;115:179-185.
[PUBMED](#) | [CROSSREF](#)
10. Brockow K, Romano A, Aberer W, Bircher AJ, Barbaud A, Bonadonna P, et al. Skin testing in patients with hypersensitivity reactions to iodinated contrast media - a European multicenter study. *Allergy* 2009;64:234-241.
[PUBMED](#) | [CROSSREF](#)
11. Fricke-Galindo I, LLerena A, López-López M. A LL, Lopez-Lopez M. An update on HLA alleles associated with adverse drug reactions. *Drug Metab Pers Ther* 2017;32:
[CROSSREF](#)
12. Jutkowitz E, Dubreuil M, Lu N, Kuntz KM, Choi HK. The cost-effectiveness of HLA-B*5801 screening to guide initial urate-lowering therapy for gout in the United States. *Semin Arthritis Rheum* 2017;46:594-600.
[PUBMED](#) | [CROSSREF](#)
13. Wang CW, Dao RL, Chung WH. Immunopathogenesis and risk factors for allopurinol severe cutaneous adverse reactions. *Curr Opin Allergy Clin Immunol* 2016;16:339-345.
[PUBMED](#) | [CROSSREF](#)
14. Pichler WJ, Naisbitt DJ, Park BK. Immune pathomechanism of drug hypersensitivity reactions. *J Allergy Clin Immunol* 2011;127 Suppl:S74-S81.
[PUBMED](#) | [CROSSREF](#)
15. Chung SJ, Kang DY, Lee W, Lee SB, Kim S, Lee SE, et al. HLA-DRB1*15: 02 is associated with iodinated contrast media-related anaphylaxis. *Invest Radiol* 2020;55:304-309.
[PUBMED](#) | [CROSSREF](#)
16. ACR committee on Drugs and Contrast Media. ACR manual on contrast media. Reston (VA): American College of Radiology; 2012, 83.
17. Dormoy A, Froelich N, Leisenbach R, Weschler B, Cazenave JP, Tongio MM. Mono-allelic amplification of exons 2-4 using allele group-specific primers for sequence-based typing (SBT) of the HLA-A, -B and -C genes: preparation and validation of ready-to-use pre-SBT mini-kits. *Tissue Antigens* 2003;62:201-216.
[PUBMED](#) | [CROSSREF](#)
18. In JW, Roh EY, Oh S, Shin S, Park KU, Song EY. Allele and haplotype frequencies of human leukocyte antigen-A, -B, -C, -DRB1, and -DQB1 from sequence-based DNA typing data in Koreans. *Ann Lab Med* 2015;35:429-435.
[PUBMED](#) | [CROSSREF](#)
19. Christiansen C. X-ray contrast media--an overview. *Toxicology* 2005;209:185-187.
[PUBMED](#) | [CROSSREF](#)
20. Kaufman DW International Collaborative Study of Severe Anaphylaxis. Risk of anaphylaxis in a hospital population in relation to the use of various drugs: an international study. *Pharmacoepidemiol Drug Saf* 2003;12:195-202.
[PUBMED](#) | [CROSSREF](#)
21. Rosado Ingelmo A, Doña Diaz I, Cabañas Moreno R, Moya Quesada MC, García-Avilés C, García Nuñez I, et al. Clinical practice guidelines for diagnosis and management of hypersensitivity reactions to contrast media. *J Investig Allergol Clin Immunol* 2016;26:144-155.
[PUBMED](#) | [CROSSREF](#)
22. Wang Q, Sun S, Xie M, Zhao K, Li X, Zhao Z. Association between the HLA-B alleles and carbamazepine-induced SJS/TEN: a meta-analysis. *Epilepsy Res* 2017;135:19-28.
[PUBMED](#) | [CROSSREF](#)
23. Fan WL, Shiao MS, Hui RC, Su SC, Wang CW, Chang YC, et al. HLA association with drug-induced adverse reactions. *J Immunol Res* 2017;2017:3186328.
[PUBMED](#) | [CROSSREF](#)
24. Lv YD, Min FL, Liao WP, He N, Zeng T, Ma DH, et al. The association between oxcarbazepine-induced maculopapular eruption and HLA-B alleles in a northern Han Chinese population. *BMC Neurol* 2013;13:75.
[PUBMED](#) | [CROSSREF](#)
25. Böhm I, Morelli J, Nairz K, Silva Hasembank Keller P, Heverhagen JT. Myths and misconceptions concerning contrast media-induced anaphylaxis: a narrative review. *Postgrad Med* 2017;129:259-266.
[PUBMED](#) | [CROSSREF](#)
26. Romano A, Guéant-Rodriguez RM, Viola M, Gaeta F, Caruso C, Guéant JL. Cross-reactivity among drugs: clinical problems. *Toxicology* 2005;209:169-179.
[PUBMED](#) | [CROSSREF](#)
27. Seitz CS, Pfeuffer P, Raith P, Bröcker EB, Trautmann A. Radioccontrast media-associated exanthema: identification of cross-reactivity and tolerability by allergologic testing. *Eur J Radiol* 2009;72:167-171.
[PUBMED](#) | [CROSSREF](#)

28. Keller M, Lerch M, Britschgi M, Tâche V, Gerber BO, Lüthi M, et al. Processing-dependent and -independent pathways for recognition of iodinated contrast media by specific human T cells. *Clin Exp Allergy* 2010;40:257-268.
[PUBMED](#) | [CROSSREF](#)
29. Brockow K, Christiansen C, Kanny G, Clément O, Barbaud A, Bircher A, et al. Management of hypersensitivity reactions to iodinated contrast media. *Allergy* 2005;60:150-158.
[PUBMED](#) | [CROSSREF](#)
30. Munechika H, Hiramatsu Y, Kudo S, Sugimura K, Hamada C, Yamaguchi K, et al. A prospective survey of delayed adverse reactions to iohexol in urography and computed tomography. *Eur Radiol* 2003;13:185-194.
[PUBMED](#) | [CROSSREF](#)