

HLA-DRB1*08:02 Is Associated with Bucillamine-Induced Proteinuria in Japanese Rheumatoid Arthritis Patients

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ABSTRACT

BACKGROUND: Drug-induced proteinuria can occur in rheumatoid arthritis (RA) patients treated with D-penicillamine, gold salts, or bucillamine (Buc), and represents a drug hypersensitivity reaction. Striking associations of human leukocyte antigen (HLA) alleles with adverse reactions have recently been reported for many drugs.

METHODS: We investigated the association of *HLA class II* with Buc-induced proteinuria (BI-Pro) in 485 Japanese RA patients treated with Buc, of whom 25 had developed BI-Pro.

RESULTS AND CONCLUSION: This preliminary study showed a highly significant association of *DRB1*08:02* with BI-Pro ($P = 1.09 \times 10^{-6}$, corrected $P [P_c] = 1.96 \times 10^{-5}$, odds ratio [OR] 25.17, 95% confidence interval [CI] 7.98–79.38). *DQB1*04:02* was also significantly associated with increased risk of BI-Pro ($P = 2.44 \times 10^{-5}$, $P_c = 2.69 \times 10^{-4}$, OR 10.35, 95%CI 3.99–26.83). These findings provide useful information for promoting personalized medicine for RA.

KEYWORDS: bucillamine, drug-induced proteinuria, *HLA-DRB1*08:02*, rheumatoid arthritis, disease-modifying anti-rheumatic drugs

CITATION: Furukawa et al. *HLA-DRB1*08:02 Is Associated with Bucillamine-Induced Proteinuria in Japanese Rheumatoid Arthritis Patients*. *Biomarker Insights* 2014;9:23–28 doi: 10.4137/BMI.S13654.

RECEIVED: November 14, 2013. **RESUBMITTED:** January 22, 2014. **ACCEPTED FOR PUBLICATION:** January 23, 2014.

ACADEMIC EDITOR: Karen Pulford, Associate Editor

TYPE: Original Research

FUNDING: The work was supported by a grant-in-aid for scientific research (B, C) (22390199, 22591090) from the Japan Society for the Promotion of Science, health and labor science research grants from the Ministry of Health, Labour, and Welfare of Japan, grants-in-aid for clinical research from National Hospital Organization, research grants from Daiwa Securities Health Foundation, Japan Research Foundation for Clinical Pharmacology, The Nakatomi Foundation, Takeda Science Foundation, Mitsui Sumitomo Insurance Welfare Foundation, and also from the following pharmaceutical companies: Abbott Japan Co., Ltd., Astellas Pharma Inc., Chugai Pharmaceutical Co., Ltd., Eisai Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Merck Sharp & Dohme Corp., Pfizer Japan Inc., Takeda Pharmaceutical Company Limited, and Teijin Pharma Limited. The funders had no role in study design, data collection and analysis, decision to publish, or manuscript preparation.

COMPETING INTERESTS: The following funders are supported in whole or in part by the listed pharmaceutical companies. The Japan Research Foundation for Clinical Pharmacology is run by Daiichi Sankyo, the Takeda Science Foundation is supported by an endowment from Takeda Pharmaceutical Company, and The Nakatomi Foundation was established by Hisamitsu Pharmaceutical Co., Inc. The Daiwa Securities Health Foundation was established by Daiwa Securities Group Inc., and Mitsui Sumitomo Insurance Welfare Foundation was established by Mitsui Sumitomo Insurance Co., Ltd. ST discloses research grants from the nine pharmaceutical companies listed in the Funding section above. The other authors declare no financial or commercial conflict of interest.

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Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease, susceptibility to which is associated with genetic and environmental factors. RA is treated with disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate,

D-penicillamine, sulfasalazine, gold salts, anti-malarial drugs, and biological agents. One such DMARD is bucillamine (Buc) [(2R)-2-(2-methyl-2-sulfanylpropanoylamino)-3-sulfanylpropanoic acid], a thiol compound like D-penicillamine.^{1,2} Buc has been used for the treatment of RA in Japan for 26 years.³



It was known that drug-induced proteinuria can occur in RA patients treated with D-penicillamine or gold salts.^{4,5} Buc-induced proteinuria (BI-Pro) because of membranous nephropathy is also reported; the prevalence of BI-Pro was reported to be 5.3%.^{6,7} BI-Pro cases developed proteinuria without renal dysfunction on Buc treatment, but this disappeared after discontinuing the drug. However, the mechanism responsible remains unclear. It was suggested that tubular basement membrane and renal tubular epithelial antigens released from renal tubules damaged by thiol compounds invoke the generation of autoantibodies against them and induce membranous nephropathy.⁸ If biomarkers for predicting BI-Pro were exploited, Buc could be a more useful DMARD.

Certain human leukocyte antigen (*HLA*) alleles are known to be associated with RA in most ethnic groups,⁹ especially *HLA-DRB1*04:05* in Japanese and **04:01* in the European population. Some striking associations between HLA alleles and adverse drug reactions have been reported, such as methazolamide-induced Stevens–Johnson syndrome and *B*59:01*,¹⁰ amoxicillin–clavulanate-induced hepatitis and *DRB1*15:01*,¹¹ methimazole-induced agranulocytosis and *DRB1*08:03*,¹² or methotrexate-induced interstitial lung disease and *A*31:01*.¹³ These observations imply that HLA plays a substantial role in drug-induced hypersensitivity reactions. The molecular mechanisms underlying drug hypersensitivity associated with certain HLA alleles remain unclear. The product of the interaction of HLA molecules with drugs may directly activate T cells.¹⁴ Alternatively, drugs or their metabolites may act as haptens binding to peptides already loaded on the HLA molecules. Furthermore, a drug-modified HLA–peptide repertoire may trigger drug hypersensitivity.¹⁵ Several studies have focused on proteinuria induced by thiol compounds in RA and reported strong associations with HLA class II allele, DR3, in people of European descent.^{16,17} Here, we investigated *HLA class II* associations with proteinuria induced by the thiol compound, Buc, in Japanese RA patients.

Materials and Methods

Patients and controls. A total of 25 RA patients with episodes of BI-Pro and 460 control RA patients without any episodes of BI-Pro under Buc treatment were recruited at Sagami Hospital, Tama Medical Center, Nagasaki Medical Center, and Yokohama Minami Kyosai Hospital. BI-Pro was defined as developed proteinuria during Buc treatment that disappeared after discontinuing the drug. The proteinuria was diagnosed by spot qualitative urinalysis results. No BI-Pro case was histologically confirmed. No BI-Pro case has been complicated with other renal disorders. No BI-Pro case was treated with other DMARDs than Buc, while suffering from BI-Pro. All patients with RA were native Japanese and fulfilled the 1988 American College of Rheumatology criteria for RA.¹⁸ This study was reviewed and approved by the research ethics committees of each participating institute, namely Sagami Hospital, Nagasaki Medical Center, Yokohama Minami

Kyosai Hospital, Tama Medical Center, and University of Tsukuba. Written informed consent was obtained from all study participants. This study was conducted in accordance with the principles expressed in the Declaration of Helsinki.

Genotyping. Genotyping of *HLA class II* alleles was performed by polymerase chain reaction with sequence-specific oligonucleotide probes using WAKFlow HLA typing kits (Wakunaga, Hiroshima, Japan) and the Bio-Plex 200 system (Bio-Rad, Hercules, CA). *DRB1–DQB1* haplotypes were elucidated by direct counting. Some of the RA patients were also included in other studies that reported on susceptibility effects for interstitial lung disease.^{13,19}

Statistical analysis. Differences in RA characteristics and allele or haplotype carrier frequencies were analyzed by Fisher's exact test using 2×2 contingency tables or Mann–Whitney's *U* test. Alleles with more than 1% of the frequency in RA were tested. Adjustment for multiple comparisons was performed using the Bonferroni method. Corrected *P* (*P_c*) values were calculated by multiplying the *P* value by the number of alleles tested. The specificity, the sensitivity, the positive likelihood ratio, and the negative likelihood ratio were calculated under the dominant model. The number of persons who would need to be screened to prevent one incident of BI-Pro was also estimated from the reported prevalence of BI-Pro.⁷

Results

Characteristics of RA patients. Characteristics of RA patients are given in Table 1. Duration of Buc treatment in RA patients with episodes of BI-Pro was shorter than in the RA patients without any episodes of BI-Pro. There were no significant differences in terms of mean age, percentage of males, disease duration, Steinbrocker stage, association of secondary Sjögren's syndrome, rheumatoid factor, anti-citrullinated peptide antibody, dose of Buc, anti-Ro/SS-A antibody, anti-La/SS-B antibody, or history of methotrexate (MTX) or biologic DMARDs treatment between RA patients with episodes of BI-Pro and RA patients without any episodes of BI-Pro under Buc treatment.

Association of HLA class II allele carrier frequencies with BI-Pro. We tested whether the carrier frequencies of any *HLA* alleles were increased in RA patients with BI-Pro. A significant association was found for *HLA-DRB1*08:02* ($P = 1.09 \times 10^{-6}$, [P_c] = 1.96×10^{-5} , odds ratio [OR] 25.17, 95% confidence interval [CI] 7.98–79.38; Table 2) under the dominant model. *DQB1*04:02* was also significantly associated with increased risk of BI-Pro ($P = 2.44 \times 10^{-5}$, $P_c = 2.69 \times 10^{-4}$, OR 10.35, 95% CI 3.99–26.83; Table 2). None of the *HLA-DPB1* alleles were associated with BI-Pro (Table 2). Significant associations were also found for *DRB1*08:02* ($P = 1.65 \times 10^{-6}$, $P_c = 2.98 \times 10^{-5}$, OR 21.23, 95% CI 7.13–63.24) and *DQB1*04:02* ($P = 3.99 \times 10^{-5}$, $P_c = 4.39 \times 10^{-4}$, OR 8.57, 95% CI 3.57–20.59) under the allele model.

The specificity of the marker is 98.5% and the sensitivity is 28.0%, according to the dominant model. The positive

Table 1. Characteristics of RA patients.

	BI-PRO(+)	BI-PRO(-)	P
Number	25	460	
Mean age, years (SD)	65.3 (12.5)	64.3 (10.8)	0.9295*
Male, n (%)	2 (8.0)	77 (16.7)	0.4026
Disease duration, years (SD)	12.9 (8.8)	16.4 (10.7)	0.1776*
Steinbrocker stages III and IV, n (%)	12 (48.0)	286 (62.2)	0.6489
Association of secondary SS, n (%)	4 (16.0)	31 (6.7)	0.0966
Rheumatoid factor positive, n (%)	21 (84.0)	407 (88.5)	0.2500
ACPA positive, n (%)	20 (80.0)	414 (90.0)	0.3858
Dose of Buc, mg (SD)	150 (68)	157 (65)	0.8235*
Duration of Buc treatment, years (SD)	0.6 (0.5)	2.4 (3.2)	0.0016*
Anti-Ro/SS-A antibody positive, n (%)	4 (16.0)	81 (17.6)	1.0000
Anti-La/SS-B antibody positive, n (%)	2 (8.0)	13 (2.8)	0.0725
History of MTX treatment, n (%)	11 (44.0)	299 (65.0)	0.0519
History of biologic DMARDs treatment, n (%)	6 (24.0)	123 (26.7)	1.0000

Note: *Mann–Whitney's *U* test was employed.

Abbreviations: RA, rheumatoid arthritis; BI-Pro(+), RA with bucillamine-induced proteinuria; BI-Pro(-), RA without bucillamine-induced proteinuria; SS, Sjögren's syndrome; ACPA, anti-citrullinated peptide antibody; Buc, bucillamine; MTX, methotrexate; DMARDs, disease-modifying anti-rheumatic drugs. Association was tested by Fisher's exact test using 2 × 2 contingency tables or Mann–Whitney's *U* test.

likelihood ratio of *DRB1*08:02* is 18.4, and the negative likelihood ratio is 0.731. On the basis of the prevalence of BI-Pro,⁷ the presence of *DRB1*08:02* increases the risk of BI-Pro to 50.5%, whereas its absence reduces the risk to 3.9%. The number of persons who would need to be screened to prevent one incident of BI-Pro is 74.

Role of the *DRB1*08:02–DQB1*04:02* haplotype. The *DRB1* and *DQB1* alleles that showed significant association are in strong linkage disequilibrium ($D' = 0.625$, $r^2 = 0.192$ for *DRB1*08:02–DQB1*04:02* in RA patients treated with Buc). To elucidate which of the *DRB1* and *DQB1* was responsible for the association, haplotype analysis of *DRB1–DQB1* was performed. *DRB1*08:02–DQB1*04:02* was significantly associated with BI-Pro (n = 6 [24.0%] in RA with BI-Pro vs. n = 3 [0.7%] in RA without BI-Pro, $P = 7.65 \times 10^{-7}$, OR 48.11, 95% CI 11.17–207.12), but *DRB1*08:02–DQB1*03:02* (n = 1 [4.0%] in RA with BI-Pro vs. n = 4 [0.9%] in RA without BI-Pro, $P = 0.2334$, OR 4.75) or *DRB1*04:10–DQB1*04:02* (n = 2 [8.0%] in RA with BI-Pro vs. n = 17 [3.7%] in RA without BI-Pro, $P = 0.2558$, OR 2.27) were not. The two-locus analysis was also performed to clarify the primary role of *DRB1*08:02* or *DQB1*04:02*. OR for *DRB1*08:02* in the patients without *DQB1*04:02* was 6.81, whereas OR for

*DQB1*04:02* in the patients without *DRB1*08:02* was 3.21 (Table 3). The difference did not reach statistical significance, because the strong linkage disequilibrium between *DRB1*08:02* and *DQB1*04:02* causes low frequency of *DRB1*08:02* in the patients without *DQB1*04:02* and that of *DQB1*04:02* in the patients without *DRB1*08:02*. Thus, these data suggested the role of the *DRB1*08:02–DQB1*04:02* haplotype.

Discussion

Several studies have shown that *HLA* polymorphism contributes to susceptibility to adverse drug reactions.^{4,5,20} To the best of our knowledge, the present report is the first to show an association of *DRB1*08:02* with BI-Pro in Japanese RA patients. *DRB1*08:02* would be a useful clinical marker to prevent BI-Pro. Its prevention has crucial significance for the safety of clinical practice in RA. Thus, these findings provide useful information for promoting personalized medicine for RA.

The RA patients with secondary Sjögren's syndrome or anti-Ro/SS-A antibodies are more prone to develop adverse effects when treated with DMARDs.^{21–23} The HLA-DR3 allele is strongly associated with the presence of anti-Ro/SS-A antibodies in patients of European descent.²⁴ These data explain the strong association of HLA-DR3 with drug-induced proteinuria in European RA patients.^{16,17} A recent study has shown that the frequency of the *DRB1*08:03* allele is significantly higher in Japanese RA patients with anti-Ro/SS-A antibodies than in those without, and that the frequency of *DRB1*08:02* is also higher, but not statistically significantly so.²⁵ However, the frequency of *DRB1*08:03* was not higher in RA patients with BI-Pro, but *DRB1*08:02* was (Tables 2). In our study, 4 of 25 RA patients with BI-Pro were associated with secondary Sjögren's syndrome and the frequency was higher than that in RA patients without BI-Pro, though the difference did not reach significance (Table 1). In addition, 4 of 25 RA patients with BI-Pro were positive for anti-Ro/SS-A antibodies and the frequency was similar to that in RA patients without episode of BI-Pro (Table 1). Therefore, anti-Ro/SS-A antibodies in RA patients would not be a marker for BI-Pro in Japanese patients. This preliminary study showed a highly significant association of *DRB1*08:02* with BI-Pro, although the sample size of the study is small and the selection bias could not be avoided in retrospective case–control studies. Therefore, the association needs confirmation in future large-scale prospective studies. We also cannot rule out the possibility that other genes causing these reactions might reside in the *HLA* region in linkage disequilibrium with the *DRB1*08:02–DQB1*04:02* haplotype. This possibility could be addressed by re-sequencing the entire *HLA* region of the haplotype.

Conclusion

To our knowledge, this is the first identification of an association of the *DRB1*08:02* allele with susceptibility to BI-Pro

**Table 2.** HLA allele carrier frequency in the RA patients with or without BI-Pro.

	BI-PRO(+) N = 25	BI-PRO(-) N = 460	P	OR	P _c	95%CI
DRB1*0101	3 (12.0)	65 (14.1)	1.0000	0.83	NS	
DRB1*0401	3 (12.0)	30 (6.5)	0.2374	1.95	NS	
DRB1*0403	1 (4.0)	9 (2.0)	0.4139	2.09	NS	
DRB1*0405	10 (40.0)	236 (51.3)	0.3085	0.63	NS	
DRB1*0406	0 (0.0)	19 (4.1)	0.6145	0.44	NS	
DRB1*0410	2 (8.0)	20 (4.3)	0.3153	1.91	NS	
DRB1*0802	7 (28.0)	7 (1.5)	1.09 × 10 ⁻⁶	25.17	1.96 × 10 ⁻⁵	(7.98–79.38)
DRB1*0803	1 (4.0)	45 (9.8)	0.4962	0.38	NS	
DRB1*0901	10 (40.0)	125 (27.2)	0.1730	1.79	NS	
DRB1*1101	0 (0.0)	15 (3.3)	1.0000	0.56	NS	
DRB1*1201	2 (8.0)	35 (7.6)	1.0000	1.06	NS	
DRB1*1202	0 (0.0)	9 (2.0)	1.0000	0.93	NS	
DRB1*1302	2 (8.0)	41 (8.9)	1.0000	0.89	NS	
DRB1*1403	1 (4.0)	7 (1.5)	0.3472	2.70	NS	
DRB1*1406	1 (4.0)	13 (2.8)	0.5283	1.43	NS	
DRB1*1454	0 (0.0)	28 (6.1)	0.3861	0.30	NS	
DRB1*1501	1 (4.0)	51 (11.1)	0.5016	0.33	NS	
DRB1*1502	2 (8.0)	80 (17.4)	0.2833	0.41	NS	
DQB1*0301	7 (28.0)	89 (19.3)	0.3034	1.62	NS	
DQB1*0302	2 (8.0)	40 (8.7)	1.0000	0.91	NS	
DQB1*0303	9 (36.0)	129 (28.0)	0.3724	1.44	NS	
DQB1*0401	10 (40.0)	243 (52.8)	0.2246	0.60	NS	
DQB1*0402	8 (32.0)	20 (4.3)	2.44 × 10 ⁻⁵	10.35	2.69 × 10 ⁻⁴	(3.99–26.83)
DQB1*0501	3 (12.0)	69 (15.0)	1.0000	0.77	NS	
DQB1*0502	1 (4.0)	25 (5.4)	1.0000	0.73	NS	
DQB1*0503	0 (0.0)	17 (3.7)	1.0000	0.50	NS	
DQB1*0601	3 (12.0)	124 (27.0)	0.1075	0.37	NS	
DQB1*0602	1 (4.0)	49 (10.7)	0.4978	0.35	NS	
DQB1*0604	2 (8.0)	37 (8.0)	1.0000	0.99	NS	
DPB1*0201	13 (52.0)	209 (45.4)	0.5428	1.30	NS	
DPB1*0202	3 (12.0)	46 (10.0)	0.7308	1.23	NS	
DPB1*0301	3 (12.0)	32 (7.0)	0.4125	1.82	NS	
DPB1*0401	2 (8.0)	36 (7.8)	1.0000	1.02	NS	
DPB1*0402	9 (36.0)	100 (21.7)	0.1357	2.03	NS	
DPB1*0501	12 (48.0)	275 (59.8)	0.2969	0.62	NS	
DPB1*0901	2 (8.0)	62 (13.5)	0.7595	0.56	NS	
DPB1*1301	0 (0.0)	13 (2.8)	1.0000	0.65	NS	
DPB1*1401	0 (0.0)	17 (3.7)	1.0000	0.50	NS	

Notes: Alleles with more than 1% of the frequency in RA were tested. Allele carrier frequencies are shown in parenthesis (%). Significance of associations was tested by Fisher's exact test using 2 × 2 contingency tables.

Abbreviations: HLA, human leukocyte antigen; RA, rheumatoid arthritis; BI-Pro, bucillamine-induced proteinuria; BI-Pro(+), RA with BI-Pro; BI-Pro(-), RA without BI-Pro; OR, odds ratio; CI, confidence interval; P_c, corrected P value; NS, not significant.

Table 3. HLA allele carrier frequency in the RA cases with or without specific alleles.

SPECIFIC ALLELES	BI-PRO(+)		BI-PRO(-)		P	OR	P _c	95%CI
	DRB1*08:02(+)	DRB1*08:02(-)	DRB1*08:02(+)	DRB1*08:02(-)				
DQB1*04:02(+)	6 (75.0)	2 (25.0)	3 (15.0)	17 (85.0)	0.0048	17.00	0.0872	(2.26–127.75)
DQB1*04:02(-)	1 (5.9)	16 (94.1)	4 (0.9)	436 (99.1)	0.1734	6.81	NS	
DRB1*08:02(+)	6 (85.7)	1 (14.3)	3 (42.9)	4 (57.1)	0.2657	8.00	NS	
DRB1*08:02(-)	2 (11.1)	16 (88.9)	17 (3.8)	436 (96.2)	0.1606	3.21	NS	

Notes: Association was tested by Fisher's exact test using 2 × 2 contingency tables.

Abbreviations: HLA, human leukocyte antigen; RA, rheumatoid arthritis; BI-Pro, bucillamine-induced proteinuria; BI-Pro(+), RA with BI-Pro; BI-Pro(-), RA without BI-Pro; OR, odds ratio; CI, confidence interval; P_c, corrected P value. Allele carrier frequencies are shown in parenthesis (%).

in Japanese RA patients. Our findings support a role for *DRB1*08:02* in BI-Pro pathogenesis and its potential clinical usefulness as a biomarker.

Acknowledgment

We thank Ms. Mayumi Yokoyama (Sagamihara Hospital) for secretarial assistance.

Author Contributions

HF, NT, and ST conceived and designed the experiments. HF and SO performed the experiments. HF analyzed the data. HF, KS, SS, AH, AK, NF, TM, KM, AS, SN, and ST contributed reagents/materials/analysis tools. HF, NT, and ST wrote the manuscript. All authors reviewed and approved the final manuscript.

DISCLOSURES AND ETHICS

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

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