ARTHRITIS & RHEUMATISM
Vol. 64, No. 11, November 2012, pp 3736–3740
DOI 10.1002/art.34657

BRIEF REPORT

Association of HLA–DRB1*0101/*0405 With Susceptibility to Anti–Melanoma Differentiation–Associated Gene 5 Antibody–Positive Dermatomyositis in the Japanese Population

Takahisa Gono,[1] Yasushi Kawaguchi,[1] Masataka Kuwana,[2] Tomoko Sugiura,[1] Takefumi Furuya,[1] Kae Takagi,[1] Hisae Ichida,[1] Yasuhiro Katsumata,[1] Masanori Hanaoka,[1] Yuko Ota,[1] and Hisashi Yamanaka[1]

Objective. **The complication of interstitial lung disease (ILD) in polymyositis/dermatomyositis (PM/DM) is associated with anti–aminoacyl–transfer RNA synthetase (anti-aaRS) antibody or anti–melanoma differentiation–associated gene 5 (anti–MDA-5) antibody positivity. Anti–MDA-5 antibody is associated with clinically amyopathic DM and fatal outcome due to rapidly progressive ILD in Asian populations. The association between genetic factors and anti–MDA-5 antibody–positive DM is unclear. This study was undertaken to investigate the HLA–DRB1 genotype in patients with anti–MDA-5 antibody–positive DM.**

Methods. **We examined genetic differences among 17 patients with anti–MDA-5 antibody–positive DM, 33 patients with anti-aaRS antibody–positive PM/DM, 33 patients with PM/DM without anti-aaRS antibody or ILD, and 265 healthy controls.**

Results. **The frequencies of HLA–DRB1*0101 and DRB1*0405 were 29% and 71%, respectively, in patients with anti–MDA-5 antibody–positive DM, which were higher than the frequencies in healthy controls (10% and 25%, respectively). Among the 17 patients with anti–MDA-5 antibody–positive DM, 16 (94%) harbored either the DRB1*0101 or DRB1*0405 allele. The combined frequency of the DRB1*0101 allele and the DRB1*0405 allele was significantly higher in patients with anti–MDA-5 antibody–positive DM than in patients with PM/DM without anti-aaRS antibody or ILD, with an odds ratio (OR) of 42.7 (95% confidence interval [95% CI] 4.9–370.2) ($P = 1.1 \times 10^{-5}$), or in patients with anti-aaRS antibody–positive PM/DM (OR 13.3 [95% CI 1.6–112.6], $P = 4.5 \times 10^{-3}$).**

Conclusion. **Our findings indicate that HLA–DRB1*0101/*0405 is associated with susceptibility to anti–MDA-5 antibody–positive DM in the Japanese population.**

Dermatomyositis (DM) is characterized by inflammation of the skin and muscle (1) and is occasionally complicated by interstitial lung disease (ILD). In particular, rapidly progressive ILD is an intractable and life-threatening complication. Clinically amyopathic DM (CADM) includes typical skin lesions with amyopathy or hypomyopathy (2). It has recently been reported that patients with CADM who are positive for the anti–melanoma differentiation–associated gene 5 (MDA-5) antibody frequently have complications with rapidly progressive ILD, especially in the Japanese population (3–5). In general, anti–MDA-5 antibody is specific for rapidly progressive ILD associated with CADM and is not detected in patients with CADM or DM without ILD or in patients with polymyositis (PM). The MDA-5 protein plays a role in the innate immune system. MDA-5 initially recognizes picornaviruses, such as coxsackievirus, and induces antiviral responses by producing type I interferons and tumor necrosis factor α (6). Hyperferritinemia is complicated by rapidly progressive ILD in anti–MDA-5 antibody–positive DM (4,5). Although the pathogenesis of rapidly progressive ILD associated with anti–MDA-5 antibody–positive DM has been tentatively attributed to a cytokine storm triggered

Supported by a research grant from the Ministry of Health, Labor, and Welfare of Japan.

[1]Takahisa Gono, MD, PhD, Yasushi Kawaguchi, MD, PhD, Tomoko Sugiura, MD, PhD, Takefumi Furuya, MD, PhD, Kae Takagi, MD, PhD, Hisae Ichida, MD, Yasuhiro Katsumata, MD, Masanori Hanaoka, MD, Yuko Ota, MD, Hisashi Yamanaka, MD, PhD: Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan; Masataka Kuwana, MD, PhD: Keio University School of Medicine, Tokyo, Japan.

Dr. Kuwana holds a patent on an anti–MDA-5 antibody measuring kit.

Address correspondence to Yasushi Kawaguchi, MD, PhD, Institute of Rheumatology, Tokyo Women's Medical University, 10-22 Kawada-cho, Shinjuku-Ku, Tokyo 162-0054, Japan. E-mail: y-kawa@ior.twmu.ac.jp.

Submitted for publication March 24, 2012; accepted in revised form July 26, 2012.

by viral infection, especially in the skin and lungs, its exact mechanism is unknown.

In PM/DM, complication with ILD is associated with the anti–aminoacyl–transfer RNA synthetase (anti-aaRS) antibody or anti–MDA-5 antibody. It has been reported that 90% of Caucasian patients with the anti-aaRS antibody are carriers of HLA–DRB1*03 (7). In the Japanese population, HLA–DRB1*0405 is associated with susceptibility to anti-aaRS antibody–positive PM/DM (8). However, associations between genetic factors and anti–MDA-5 antibody–positive DM have remained unclear.

Therefore, we investigated the HLA–DRB1 gene in patients with anti–MDA-5 antibody–positive DM. In addition, we compared genetic differences in HLA among patients with anti–MDA-5 antibody–positive DM, patients with anti-aaRS antibody–positive PM/DM, and patients with PM/DM without anti-aaRS antibody or ILD.

Table 1. Clinical characteristics and HLA–DRB1 genotype of the patients with anti–MDA-5 antibody–positive DM*

Patient/age/sex	Genotype	Phenotype	ILD type
1/48/M	DRB1*0101/1602	CADM	Rapidly progressive
2/25/F	DRB1*0101/1501	CADM	Chronic
3/53/F	DRB1*0101/0803	CADM	Rapidly progressive
4/18/M	DRB1*0101/1502	CADM	Rapidly progressive
5/47/F	DRB1*0101/0405	DM	Rapidly progressive
6/58/M	DRB1*0405/1406	CADM	Rapidly progressive
7/16/F	DRB1*0405/0401	CADM	Rapidly progressive
8/53/F	DRB1*0405/1501	CADM	Rapidly progressive
9/53/F	DRB1*0405/0410	CADM	Rapidly progressive
10/44/F	DRB1*0405/1406	CADM	Chronic
11/45/F	DRB1*0405/1202	CADM	Chronic
12/39/M	DRB1*0405/0401	CADM	Chronic
13/47/F	DRB1*0405/1201	CADM	Chronic
14/76/F	DRB1*0405/0802	CADM	Rapidly progressive
15/56/F	DRB1*0405/1502	CADM	Rapidly progressive
16/43/M	DRB1*0405/0901	CADM	Chronic
17/66/F	DRB1*0901/1502	CADM	Rapidly progressive

* Anti–MDA-5 = anti–melanoma differentiation–associated gene 5; DM = dermatomyositis; ILD = interstitial lung disease; CADM = clinically amyopathic DM.

PATIENTS AND METHODS

Patients. This retrospective study included patients admitted to Tokyo Women's Medical University Aoyama Hospital or Keio University Hospital from August 1992 to February 2010. Medical records were obtained for 142 and 57 patients diagnosed as having DM and CADM, respectively. The anti–MDA-5 antibody was detected in 31 patients. DNA samples were available for 17 patients with the anti–MDA-5 antibody, and all of these patients were enrolled in the study. All of the enrolled patients had skin rashes, myopathy, or respiratory symptoms (or a combination thereof) at admission. The patients were diagnosed as having DM or CADM based on the criteria of Bohan and Peter (9) or Sontheimer (10), respectively. Specific rashes, including heliotrope rash, Gottron's sign, or Gottron's papules, were used to define DM or CADM. In general, CADM patients present with typical skin lesions and amyopathy or hypomyopathy with a duration of >6 months. A subset of the CADM group included patients who developed fatal ILD within the first 6 months of this study. Clinical data were obtained from hospital admission records.

To investigate the characteristics of the HLA–DRB1 genotype in anti–MDA-5 antibody–positive DM, HLA data were obtained in patients with anti-aaRS antibody–positive PM/DM, patients without anti-aaRS antibody or ILD, and healthy controls. These HLA genotype databases have been described previously (8). All of the subjects in the present study were Japanese. None of the subjects had rheumatoid arthritis (RA) or other connective tissue diseases. This study was approved by the ethics committee of Tokyo Women's Medical University and was performed in accordance with the Declaration of Helsinki.

Evaluation of autoantibodies. Anti–MDA-5 antibody was detected by immunoprecipitation (IP) assay and enzyme-linked immunosorbent assay using recombinant MDA-5 as an antigen, as previously described (3). Anti-aaRS antibodies, including Jo-1, EJ, PL-7, PL-12, and OJ; anti–signal recognition particle (anti-SRP) antibody; anti-Ku antibody; and anti–U1 small nuclear RNP (anti-U1 snRNP) antibody were assessed by RNA IP assays.

Classification of ILD. Patients were evaluated for ILD by chest radiography and computed tomography (CT) or high-resolution CT of the chest. Rapidly progressive ILD was defined as a progressive ILD within 3 months of the onset of respiratory symptoms. Chronic ILD was defined as ILD that was asymptomatic and non–rapidly progressive or slowly progressive over 3 months (11).

HLA–DRB1 genotyping. HLA–DRB1 genotyping was performed using polymerase chain reaction–reverse sequence-specific oligonucleotide techniques and standard methods. The DNA for the HLA–DRB1 genotyping of the patients was extracted from peripheral blood mononuclear cells using standard methods.

Statistical analysis. The chi-square test was used for the comparison of frequencies, and Fisher's exact test was used when appropriate. Data were analyzed using JMP software (SAS Institute). *P* values were adjusted by Bonferroni correction when appropriate.

RESULTS

Clinical characteristics and HLA–DRB1 genotype of patients with anti–MDA-5 antibody–positive DM. As shown in Table 1, 17 patients with anti–MDA-5 antibody–positive DM were enrolled in the study. Their mean ± SD age was 46 ± 16 years. Seventy-one percent were women. The HLA–DRB1*0101 and DRB1*0405 alleles were identified in 5 patients (29%) and 12 patients (71%), respectively. The HLA–DRB1*0101 or *0405 allele was identified in 16 (94%) of the 17

Table 2. Comparison of HLA–DRB1 genotypes among patients with anti–MDA-5 antibody–positive DM, patients with anti-aaRS antibody–positive PM/DM, and patients with PM/DM without anti-aaRS antibody or ILD*

Genotype	Patients with anti–MDA-5 antibody–positive DM (n = 17)	Patients with anti-aaRS antibody–positive PM/DM		Patients with PM/DM without anti-aaRS antibody or ILD		Healthy controls (n = 265)
		PM/DM (n = 33)	DM (n = 19)	PM/DM (n = 33)	DM (n = 21)	
DRB1*0101	29	12	11	12	14	10
DRB1*0401	12	0	0	3	5	2
DRB1*0403	0	9	5	6	5	5
DRB1*0405	71†	42	53	18	24	25
DRB1*0406	0	6	5	3	5	7
DRB1*0407	0	0	0	0	0	2
DRB1*0410	6	3	5	9	5	2
DRB1*0802	6	18	21	9	10	7
DRB1*0803	6	24	21	27	19	14
DRB1*0901	12	24	21	18	19	30
DRB1*1101	0	3	0	0	0	2
DRB1*1201	6	9	16	3	5	7
DRB1*1202	6	6	0	0	0	4
DRB1*1301	0	0	0	3	0	0
DRB1*1302	0	6	5	21	29	19
DRB1*1401	0	3	5	9	10	5
DRB1*1403	0	3	0	6	10	4
DRB1*1405	0	3	5	3	5	6
DRB1*1406	12	0	0	3	5	3
DRB1*1501	12	12	16	9	5	11
DRB1*1502	18	6	11	21	24	20
DRB1*1602	6	0	0	6	0	3
Other	0	0	0	0	0	5

* Values are the percent of subjects. Anti-aaRS = anti–aminoacyl–transfer RNA synthetase; PM = polymyositis (see Table 1 for other definitions).
† $P = 0.0003$ versus patients with PM/DM without anti-aaRS antibody or ILD; $P = 0.00018$ versus healthy controls.

patients. No patients had homoalleles of HLA–DRB1*0101 or DRB1*0405. One patient had both DRB1*0101 and DRB1*0405. With respect to the clinical phenotype, 16 patients had CADM. ILD complication was observed in all of the patients. Moreover, the frequency of rapidly progressive ILD was high (65%). No patients had RA or other connective tissue diseases as complications.

Comparison of the HLA–DRB1 genotype in patients with anti–MDA-5 antibody–positive DM, patients with anti-aaRS antibody–positive PM/DM, and patients with PM/DM without anti-aaRS antibody or ILD. To investigate the characteristics of the HLA–DRB1 genotype in anti–MDA-5 antibody–positive DM, the frequency of the HLA–DRB1 genotype was compared among patients with anti–MDA-5 antibody–positive DM, patients with anti-aaRS antibody–positive PM/DM, patients with PM/DM without anti-aaRS antibody or ILD, and healthy controls (Table 2).

Data previously obtained at our institution indicated that 33 PM/DM patients (14 patients with PM and 19 with DM) exhibited anti-aaRS antibody, as follows: 8 PM patients and 8 DM patients had anti–Jo-1; 4 PM patients and 6 DM patients had anti-EJ; 2 PM patients and 2 DM patients had anti–PL-7; 0 PM patients and 3 DM patients had anti–PL-12; and none of the patients had anti-OJ. Of the 33 patients with anti-aaRS antibody–positive PM/DM, 24 (73%) had ILD. Moreover, 33 PM/DM patients (12 PM patients and 21 DM patients) had neither anti-aaRS antibody nor ILD, and in all 21 of these DM patients, the clinical phenotype was classic DM, not CADM. In patients with PM/DM without anti-aaRS antibody or ILD, anti-SRP antibody, anti-U1 snRNP antibody, and anti-Ku antibody were detected in 3 PM patients, 1 DM patient, and 0 patients, respectively.

As shown in Table 2, the frequency of HLA–DRB1*0101 was ~30% in anti–MDA-5 antibody–positive DM and ~10% in the other subsets, although the difference was not significant ($P = 0.012$ versus

Table 3. Frequency of the HLA–DRB1*0101/0405 alleles in patients with anti–MDA-5 antibody–positive DM*

	Patients with anti–MDA-5 antibody–positive DM (n = 17)	Patients with anti-aaRS antibody–positive PM/DM		Patients with PM/DM without anti-aaRS antibody or ILD	
		PM/DM (n = 33)	DM (n = 19)	PM/DM (n = 33)	DM (n = 21)
DRB1*0101 or DRB1*0405, %	94	55	63	27	33
P†	–	4.5×10^{-3}	4.4×10^{-2}	1.1×10^{-5}	2.0×10^{-4}
OR (95% CI)	–	13.3 (1.6–112.6)	9.3 (1.0–86.4)	42.7 (4.9–370.2)	32 (3.5–293.1)

* Anti-aaRS = anti–aminoacyl–transfer RNA synthetase; PM = polymyositis; OR = odds ratio; 95% CI = 95% confidence interval (see Table 1 for other definitions).
† Versus patients with anti–MDA-5 antibody–positive DM.

healthy controls, adjusted P value not significant). P values with Bonferroni correction for multiple comparisons less than 0.0023 were considered significant; this was determined by dividing the P value of 0.05 by 22 (the number of HLA genotypes). The inadequate statistical power may be attributed to small sample sizes. Moreover, the frequency of HLA–DRB1*0405 was significantly higher in the patients with anti–MDA-5 antibody–positive DM than in the patients with PM/DM without anti-aaRS antibody or ILD ($P = 0.0003$) or in the healthy controls ($P = 0.00018$). The frequency of HLA–DRB1*0405 was also high in patients with anti-aaRS antibody–positive PM/DM, although it was not significantly different from that in the other subsets. No significant differences were found regarding the frequencies of the other alleles.

Frequency of HLA–DRB1*0101/*0405 in patients with anti–MDA-5 antibody–positive DM compared with other PM/DM patient subsets. In this study, the HLA–DRB1*0101 or *0405 allele was identified in all but 1 of the 17 anti–MDA-5 antibody–positive patients. In the HLA–DRB1 alleles, residues 70–74 of the DRβ chain form the third hypervariable region, an important region for antigen presentation. This amino acid sequence is QRRAA, which is a shared epitope motif in both DRB1*0101 and DRB1*0405. We speculated that QRRAA may be a critical sequence in the pathophysiology of anti–MDA-5 antibody–positive DM. We considered the role of both DRB1*0101 and DRB1*0405 in anti–MDA-5 antibody–positive DM. Therefore, the combined frequency of the DRB1*0101 allele and the DRB1*0405 allele was compared among patients with anti–MDA-5 antibody–positive DM, patients with anti-aaRS antibody–positive PM/DM, and patients with PM/DM without anti-aaRS antibody or ILD.

As shown in Table 3, the combined frequency of DRB1*0101 and *0405 was significantly higher in patients with anti–MDA-5 antibody–positive DM than in patients with PM/DM without anti-aaRS antibody or ILD, with an odds ratio (OR) of 42.7 (95% confidence interval [95% CI] 4.9–370.2, $P = 1.1 \times 10^{-5}$), or in patients with DM without anti-aaRS antibody or ILD (OR 32 [95% CI 3.5–293.1], $P = 2 \times 10^{-4}$). The combined frequency of DRB1*0101 and *0405 was also higher in patients with anti–MDA-5 antibody–positive DM than in patients with anti-aaRS antibody–positive PM/DM (OR 13.3 [95% CI 1.6–112.6], $P = 4.5 \times 10^{-3}$) and patients with anti-aaRS antibody–positive DM (OR 9.3 [95% CI 1.0–86.4], $P = 4.4 \times 10^{-2}$). Moreover, the frequency of these alleles was higher in patients with anti-aaRS antibody–positive PM/DM than in patients with PM/DM without anti-aaRS antibody or ILD (OR 3.2 [95% CI 1.1–8.9], $P = 2.4 \times 10^{-2}$).

DISCUSSION

We have demonstrated an association between a genetic factor and anti–MDA-5 antibody–positive DM. Specifically, this study shows that HLA–DRB1*0101/*0405 is associated with susceptibility to anti–MDA-5 antibody–positive DM. HLA–DRB1*0301 is associated with susceptibility to anti-aaRS antibody–positive PM/DM in Caucasians. In contrast, the frequency of HLA–DRB1*0301 is low, but the frequency of HLA–DRB1*0405 is relatively high, at ~20%, in the Japanese population. HLA–DRB1*0405 is associated with susceptibility to anti-aaRS antibody–positive PM/DM in the Japanese population, whereas HLA–DRB1*0101 is not (8). In the present study, the frequency of HLA–DRB1*0405 was high in both anti–MDA-5 antibody–positive DM and anti-aaRS antibody–positive PM/DM. In contrast, the frequency of HLA–DRB1*0405 among patients with PM/DM without anti-aaRS antibody or ILD was similar to that in healthy controls. Type 1

diabetes mellitus, Vogt-Koyanagi-Harada disease, and autoimmune hepatitis have also been associated with HLA–DRB1*0405 in the Japanese population (12–14). HLA–DRB1*0405 may contribute to the pathophysiology of several autoimmune diseases.

In addition, this study revealed that the frequency of HLA–DRB1*0101 was higher in patients with anti–MDA-5 antibody–positive DM than in patients with anti-aaRS antibody–positive PM/DM or patients with PM/DM without anti-aaRS antibody or ILD, although the number of enrolled patients was small. Previously, the HLA–DRB1*01 and *04 alleles were shown to play roles in the susceptibility to and progression of RA (15). Specifically, these alleles are associated with anti–citrullinated protein antibody (ACPA)–positive RA. Residues 70–74 of the DRβ chain (QRRAA) in both HLA–DRB1*0101 and DRB1*0405 constitute an important region for antigen presentation. QRRAA may indirectly influence outcome via ACPA production (15). Among PM/DM patients in the Japanese population, HLA–DRB1*0101 or *0405 can also be associated with the production of autoantibodies against MDA-5 or aaRS. QRRAA may be a critical sequence in the pathophysiology of anti–MDA-5 antibody–positive DM and anti-aaRS antibody–positive PM/DM. These antibodies are strongly associated with the development of ILD in PM/DM.

The HLA class II haplotypes are more important than individual alleles. DQB1 and DPB1 should be investigated in all of the patients and healthy donors included in this study. However, DQB1 and DPB1 alleles were not sufficiently investigated in all samples. This was a limitation of the present study. We plan to analyze the HLA class II haplotypes in patients with anti–MDA-5 antibody–positive DM in a future study.

In conclusion, HLA–DRB1*0101/*0405 is associated with susceptibility to anti–MDA-5 antibody–positive DM in the Japanese population. These alleles were also associated with ILD in patients with PM/DM.

ACKNOWLEDGMENTS

The authors thank Manabu Kawamoto and Mika Fujita for excellent technical assistance.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Kawaguchi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Gono, Kawaguchi, Yamanaka.
Acquisition of data. Gono, Kuwana, Furuya, Takagi, Ichida, Katsumata, Hanaoka, Ota.
Analysis and interpretation of data. Gono, Kawaguchi, Sugiura, Katsumata.

REFERENCES

1. Callen J. Dermatomyositis. Lancet 2000;355:53–7.
2. Gerami P, Schope J, McDonald L, Walling H, Sontheimer R. A systematic review of adult-onset clinically amyopathic dermatomyositis (dermatomyositis siné myositis): a missing link within the spectrum of the idiopathic inflammatory myopathies. J Am Acad Dermatol 2006;54:597–613.
3. Sato S, Hoshino K, Satoh T, Fujita T, Kawakami Y, Fujita T, et al. RNA helicase encoded by melanoma differentiation–associated gene 5 is a major autoantigen in patients with clinically amyopathic dermatomyositis: association with rapidly progressive interstitial lung disease. Arthritis Rheum 2009;60:2193–200.
4. Nakashima R, Imura Y, Kobayashi S, Yukawa N, Yoshifuji H, Nojima T, et al. The RIG-I-like receptor IFIH1/MDA5 is a dermatomyositis-specific autoantigen identified by the anti-CADM-140 antibody. Rheumatology (Oxford) 2010;49:433–40.
5. Gono T, Kawaguchi Y, Satoh T, Kuwana M, Katsumata Y, Takagi K, et al. Clinical manifestation and prognostic factor in anti-melanoma differentiation-associated gene 5 antibody-associated interstitial lung disease as a complication of dermatomyositis. Rheumatology (Oxford) 2010;49:1713–9.
6. Takeuchi O, Akira S. MDA5/RIG-I and virus recognition. Curr Opin Immunol 2008;20:17–22.
7. Goldstein R, Duvic M, Targoff IN, Reichlin M, McMenemy AM, Reveille JD, et al. HLA-D region genes associated with autoantibody responses to histidyl-transfer RNA synthetase (Jo-1) and other translation-related factors in myositis. Arthritis Rheum 1990;33:1240–8.
8. Furuya T, Hakoda M, Tsuchiya N, Kotake S, Ichikawa N, Nanke Y, et al. Immunogenetic features in 120 Japanese patients with idiopathic inflammatory myopathy. J Rheumatol 2004;31:1768–74.
9. Bohan A, Peter J. Polymyositis and dermatomyositis (first of two parts). N Engl J Med 1975;292:344–7.
10. Sontheimer R. Would a new name hasten the acceptance of amyopathic dermatomyositis (dermatomyositis siné myositis) as a distinctive subset within the idiopathic inflammatory dermatomyopathies spectrum of clinical illness? J Am Acad Dermatol 2002;46:626–36.
11. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med 2000;161:646–64.
12. Awata T, Kuzuya T, Matsuda A, Iwamoto Y, Kanazawa Y. Genetic analysis of HLA class II alleles and susceptibility to type 1 (insulin-dependent) diabetes mellitus in Japanese subjects. Diabetologia 1992;35:419–24.
13. Shindo Y, Inoko H, Yamamoto T, Ohno S. HLA–DRB1 typing of Vogt-Koyanagi-Harada's disease by PCR-RFLP and the strong association with DRB1*0405 and DRB1*0410. Br J Ophthalmol 1994;78:223–6.
14. Seki T, Ota M, Furuta S, Fukushima H, Kondo T, Hino K, et al. HLA class II molecules and autoimmune hepatitis susceptibility in Japanese patients. Gastroenterology 1992;103:1041–7.
15. Szodoray P, Szabó Z, Kapitány A, Gyetvai A, Lakos G, Szántó S, et al. Anti-citrullinated protein/peptide autoantibodies in association with genetic and environmental factors as indicators of disease outcome in rheumatoid arthritis. Autoimmun Rev 2010;9:140–3.