

Elderly Atopic Dermatitis in a Father and Daughter Associated with MHC Class II Allele HLA-DRB1*1501

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TO THE EDITOR,

The incidence of atopic dermatitis (AD) among older adults has gradually been increasing with the aging of society in developed countries [1]. In this report, we describe two cases of elderly AD in a father and daughter who underwent human leukocyte antigen (HLA) typing and analyses of filaggrin (FLG) mutations to determine the genetic background.

Case 1: A 61-year-old Japanese woman presented with a history of refractory AD since adolescence. She had complaints of allergic rhino-conjunctivitis. Her mother had no history of allergic disease. She showed lichenified eczema on the face, neck, upper trunk, upper extremities, and knee folds. She had been treated with topical corticosteroids until her 30s, but had not achieved complete remission and became fearful of using corticosteroids. She was therefore, managed using a topical moisturizer, tacrolimus, and oral antihistamines, resulting in moderate improvements.

Case 2: An 84-year-old Japanese man presented with a history of prolonged AD since his 50s. He showed lichenified eczema on the face, neck, upper trunk, and upper extremities. Immunohistochemical analysis of skin biopsy specimens showed an allergic etiology of the skin lesions, with inflammatory infiltration of numerous immunoglobulin (Ig)E-positive cells (mainly comprising IgE+CD1a+ epidermal dendritic cells, IgE+CD11c+ dermal dendritic cells and IgE+ mast cells) in the lichenified eczema [1]. He had complaints of bronchial asthma since adolescence. He also had experienced symptoms of allergic rhino-conjunctivitis and chronic obstructive pulmonary disease (COPD) since his 70s. He had been treated with topical moisturizer and tacrolimus, oral antihistamines for AD, and an oral corticosteroid, montelukast, a bronchodilator, and inhaled corticosteroid/ β -agonist for asthma and COPD, resulting in marked improvements.

HLA genotyping was mainly determined using a polymerase chain reaction (PCR)-reverse-sequence specific oligonucleotide method by the Tissue Typing Department (BML, Tokyo, Japan). In FLG genotyping, we genotyped the six loss-of-function variants (c.3321delA, p.Gln1790X, p.Ser2554X, p.Ser2889X, p.Ser3296X, and p.Lys4022X). Determination of c.3321delA was made by size, using fluorescently labeled PCR and an Applied Biosystems 3130 Genetic Analyzer (Life Technologies, Tokyo, Japan), and p.Gln1790X, p.Ser2554X, p.Ser2889X, p.Ser3296X, and p.Lys4022X using a Taqman Assay-by-Design system for single-nucleotide polymorphism genotyping (Life Technologies). Genotype results were confirmed by direct sequencing with BigDye[®] Terminator v3.1 Cycle Sequencing Kit (Life Technologies). All study protocols were approved by the ethics committees of both the Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology and the University of Tsukuba. Both patients provided written informed consent for the genetic study. Clinical characteristics and results of the genetic analyses for these two cases are summarized in **Table 1** and **Table 2**, respectively.

The comparison of clinical and genetic features between Cases 1 and 2 yielded some interesting findings. In this father and daughter pair with elderly AD, the common

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genetic background underlying the pathogenesis of AD may represent a haplotype for major histocompatibility complex (MHC) class II (i.e., HLA-DRB1*1501-DQA1*0102-DQB1*0602-DPB1*0501). The allele HLA-DRB1*1501 in this haplotype has been reported as a gene encoding an immunodominant epitope of *Dermatophagoides pteronyssinus*-1 and *D. pteronyssinus*-2, which induces sensitization of specific T cells and IgE against *D. pteronyssinus* in patients with AD [2,3] and asthma [4]. HLA-DRB1*1501/ *D. pteronyssinus*-1 and- 2 MHC class II

tetramers are therefore frequently used for clinical research in the phenotyping of house dust mite (HDM)-allergens-specific T cells in AD patients [2,3]. In addition, the alleles HLA-DQA1*0102-DQB1*0602 in this haplotype have also been reported as susceptibility genes for major antigen-presenting molecules for *D. farinae*-1-derived peptides to T cells in Japanese atopic individuals [5]. Actually, both HDM-allergens represented the major allergens in the present kindred cases.

Table 1. Clinical characteristics and laboratory findings of elderly atopic dermatitis in a father and daughter

	Case 1	Case 2
Age/sex	61/F	84/M
AD	From 15 years old	From 50 years old
Asthma	None	From 13 years old
EASI¶ / SCORAD§	29.4 / 72.1	15.5 / 29
Total IgE (IU/ml)	10,436	19,757
Specific IgEs	Positive	Positive
MAST†		
Class 6	<i>D. farinae</i> , house dust, Japanese cedar and cat	Japanese cedar and <i>Candida</i>
Class 5	Sweet vernal grass	<i>D. farinae</i>
Class 4	-	House dust
Class 3	Cypress, shrimp, <i>Candida</i> , dog and orchard	Cypress, shrimp, <i>Penicillium</i> , salmon and chicken
Class 2	Ten allergens	Eight allergens
Class 1	Three allergens	-
Class 0	Ragweed and 9 other allergens	Ragweed and 15 other allergens
CAP-FEIA‡		
Class 6	<i>D. farinae</i> , <i>D. pteronyssinus</i>	-
Class 5	-	<i>D. farinae</i> , <i>D. pteronyssinus</i>
Class 3	-	SEA, SEB
Class 0	SEA, SEB	-
PB Eosinophilia (%)	22.5	7.0
TARC (pg/ml)	3346	1244

AD, atopic dermatitis; *D. farinae*, *Dermatophagoides farinae*; *D. pteronyssinus*, *Dermatophagoides pteronyssinus*; PB, peripheral blood; SEA, staphylococcal enterotoxin A; SEB, staphylococcal enterotoxin B; TARC, thymus and activation-related chemokine

¶EASI, Eczema Area and Severity Index (maximum, 72)¹¹

§SCORAD, Severity Scoring of Atopic Dermatitis (maximum, 103)¹²

†MAST33 (BML, Tokyo, Japan): positive, class 6 (lumi count ≥ 160), 5 (lumi count 120-159), 4 (lumi count 58.1-119), 3 (lumi count 13.5-58.0) and 2 (lumi count 2.78-13.4); borderline, class 1 (lumi count 1.40-2.77); negative, class (lumi count < 1.40)

‡CAP-FEIA system (BML, Tokyo, Japan): positive, class 6 (≥ 100 UA/ml), 5 (50.0-99.9 UA/ml), 4 (17.5-49.9 UA/ml), 3 (3.50-17.49 UA/ml) and 2 (0.70-3.49 UA/ml); borderline, class 1 (0.35-0.69 UA/ml); negative, class 0 (< 0.35 UA/ml)

Table 2. Results of genetic analyses for HLA-haplotype and FLG-mutations in a father and daughter with elderly atopic dermatitis

	Case 1	Case 2
Family relation	Daughter	Father
HLA-haplotype		
Class I:	-HLA-A*2603-B*1501-C*0303; -HLA-A*3101-B*5101-C*1402	-HLA-A*2603-B*1501-C*0303; -HLA-A*0201-B*5201-C*1202
Class II:	-HLA-DRB1*1501- DQA1*0102- DQB1*0602-DPB1*0501; -HLA-DRB1*0403- DQA1*0301- DQB1*0302-DPB1*0301	-HLA-DRB1*1501- DQA1*0102- DQB1*0602-DPB1*0501; -HLA-DRB1*1502- DQA1*0103- DQB1*0601-DPB1*0901
FLG-mutations†:	None	None

HLA, human leukocyte antigen; FLG, filaggrin

†Several FLG mutations (c.3321 del A, p.Gln1790X, p.Ser2554X, p.Ser2889X, p.Ser3296X and p.Lys4022X) associated with the Japanese atopic dermatitis population^{8,9} were analyzed

HLA genotyping of the non-common haplotypes provides further information about phenotypes of AD and atopic status. The allele HLA-DPB1*0301 in another haplotype in Case 1 has been reported as a frequent genotype in Japanese patients with IgE-allergic adolescent/adult AD [6]. On the other hand, the allele HLA-DPB1*0901 in another haplotype in Case 2 has been demonstrated as a genetic risk factor for pediatric asthma among Asian populations in a genome-wide association study [7]. We consider that these genetic backgrounds might also have individually affected the clinical characteristics of kindred cases in relation to atopic skin and respiratory diseases.

The potential for a relationship between clinical manifestations and MHC class I alleles observed in the present kindred cases has not previously been reported in the literature.

FLG loss-of-function mutations were not observed in the present kindred cases of elderly AD. In a previous experimental report, at least 1 FLG-mutation (FLG null alleles R501X and 2282del4; highly significant risk factors in Caucasian populations) was found in 43% (three of seven) patients with severe adult-AD showing the HLA-DRB1*1501 allele in the United Kingdom². In younger age groups (infancy to middle age) of the Japanese population, FLG mutations (c.3321 delA, p.Ser2554X, p.Ser2889X, and/or p.Ser3296X) have been reported to be associated with AD development [8,9], elevated levels of IgE [8], and

ichthyosis vulgaris [9]. Analyses of FLG mutation in elderly patients with AD have not been widely undertaken. A previous study conducted using middle-aged to older adults (≥ 50 years old) in the United Kingdom indicated that FLG mutations (for R501X and/or 2282del4) were significantly associated with symptomatic asthma ($P=0.03$) and diagnosed eczema (probable AD, $P=0.009$) [10]. Carriers of FLG mutations showed a tendency toward early onset of the diagnosed eczema before 20 years old. However, the FLG mutations were not associated with serum levels of total IgE or specific IgEs to HDM allergens among the participants in that age population [10]. In elderly AD, late onset of AD in middle-aged to older adults is not uncommon, and the incidence of ichthyosis as a complication may be lower in patients with high levels of total and specific IgE [1]. The genetic backgrounds of AD in several phenotypes of onset and clinical characteristics may be heterogeneous. Further studies in patients with AD arising in later life in association with various phenotypes are necessary to clarify the heterogeneity of AD.

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