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Molecular sensitization patterns in birch pollen-sensitized Korean children according to the presence of oral allergy syndrome

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Abstract

The profiles of sensitization based on component-resolved diagnosis (CRD) differ from region to region in populations sensitized to birch pollen. We investigated the endotypes of birch pollen-sensitized Korean children with allergic diseases using CRD and distinguished the endotypes of oral allergy syndrome (OAS) among them.

Thirty-one birch pollen-sensitized children with allergic diseases were enrolled. Specific immunoglobulin E (IgE) to birch pollen and fruit including apple, peach, and kiwi were evaluated via skin prick tests and ImmunoCAP in all subjects. Sensitization profiles based on CRD were evaluated with the Immuno-solid-phase Allergen Chip for birch pollen-sensitization using birch pollen components (Bet v 1, Bet v 2, and Bet v 4), and for OAS using the allergen families pathogenesis-related class 10 proteins (PR-10), lipid transfer proteins, and profilin.

All patients (n = 13) with OAS were sensitive to Bet v 1. However, 61% (11/18) of patients without OAS were sensitized to Bet v 1. The level of specific IgE to Bet v 1 was higher in patients with OAS than in those without OAS. All birch pollen-sensitized Korean children with OAS were sensitized to PR-10, and 69% (9/13) of them were mono-sensitized to PR-10. Among patients without OAS, 33% (6/18) were not sensitized to any of the allergen families.

Birch pollen-sensitized Korean children with allergic diseases showed unique patterns of sensitization to Bet v 1, Bet v 2, and Bet v 4, and the sensitization profiles based on CRD were totally different according to the presence of OAS.

Abbreviations: CRD = component-resolved diagnosis, IgE = immunoglobulin E, LTP = lipid transfer proteins, OAS = oral allergy syndrome, PR-10 = pathogenesis-related class 10 proteins.

Keywords: birch pollen, food hypersensitivity, lipid transfer protein, PR-10 protein, profilin, rhinitis

1. Introduction

Birch pollen is the most common sensitizing pollen in Korea.[1] Sensitization to birch pollen has high clinical relevance in sensitized patients,[2] and is frequently associated with oral allergy syndrome (OAS).[3] OAS indicates immunoglobulin E (IgE)-mediated immediate allergy symptoms restricted to the oral mucosa caused by raw fruits and vegetables. The pathogenesis of OAS is cross-allergenicity between foods and pollen allergens,[4] and the major allergen of birch pollen, Bet v 1, exhibits cross-reactivity with many food allergens, particularly those in the Rosaceae family (e.g., apple, peach, pear, cherry, plum, and apricot).[5] Kim et al[6] reported that the prevalence of OAS is 41.7% among pollinosis patients in Korea. Apple and peach are the most common foods associated with OAS, and birch was the most common sensitizing allergen in patients with OAS.

Since, component-resolved diagnosis (CRD) using microarray technology was introduced into the field of clinical allergy, molecular-based allergy diagnostics have been used to identify a patient's reactivity to specific molecular components of allergens. These tests have been shown to have a higher specificity than *in vitro* testing with the whole allergen or skin prick tests.[7] Thus, efforts have been made to identify clinical endotypes of allergic diseases using CRD techniques.[8–12] Studies to identify the patterns of sensitization to Bet v 1, Bet v 2, and Bet v 4 in birch pollen-sensitized patients have been conducted in many countries

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and revealed that such profiles of sensitization vary from region to region.[11,12] Furthermore, studies to classify the molecular endotypes of OAS using sensitization profiles with allergen families, including pathogenesis-related class 10 proteins (PR-10), lipid transfer proteins (LTP), and profilin showed that such profiles differ between the western Mediterranean and Central/Northern Europe.[8,9]

This study was conducted to investigate the endotypes of birch pollen-sensitized Korean children with allergic diseases using CRD for Bet v 1, Bet v 2, and Bet v 4, and to distinguish the OAS endotypes among birch pollen-sensitized children using CRD for the allergen families PR-10, LTP, and profilin.

2. Methods

The children with allergic diseases who were sensitized to birch pollen were enrolled from patients aged between 3 and 15 years, who were admitted to the pediatric allergy clinic of Kangdong Sacred Heart Hospital, Hallym University, from March 2011 to September 2013.[13] Sensitization to birch pollen was defined as having an allergen-specific history with concomitant positive skin-prick tests to extracts of birch pollen or positive specific IgE to birch pollen using an ImmunoCAP assay (Phadia AB, Uppsala, Sweden). For all subjects, specific IgE for birch pollen and fruit, including apple, peach, and kiwi, were evaluated with skin-prick tests and ImmunoCAP. Specific IgE antibodies to allergen components were determined using a customized allergen microarray. Their history of allergic diseases, including atopic dermatitis, asthma, allergic rhinitis, and allergic conjunctivitis, was investigated. The diagnosis of OAS was based on a history of OAS symptoms after fruit consumption and positive results on skin prick tests or ImmunoCAP to causative fruit (apple, peach, or kiwi). Patients who were under immunotherapy or had a history of immunotherapy were excluded. This study protocol was approved by the institutional review board of the hospital (IRB number: HYI-10-44).

Skin prick tests were conducted for apple, peach, kiwi, and birch (Allergopharma, Reinbek, Germany). A positive response on skin prick tests was defined when the wheal diameter of the allergen was >3 mm and greater than the diameter of the histamine-induced wheal. The serum levels of specific IgE to birch, apple, peach, and kiwi were measured using ImmunoCAP. Results were regarded as positive when the level of specific serum IgE was 0.35 kU/L or more. Component antigen tests were conducted with Immuno-solid-phase Allergen Chip (ISAC) microarray (CRD 112; Thermo Fisher Scientific Inc., Uppsala, Sweden). The data are expressed as ISAC standardized units (ISU/L) and results were considered positive when they were >1 ISU/L.

2.1. Statistical analyses

Demographic characteristics of the study population are presented as medians with ranges in parentheses for continuous variables and as relative frequencies for categorical variables. Nonparametric variables were compared using the Mann–Whitney *U*-test and categorical values were compared using the χ^2 test. We produced receiver operating characteristic (ROC) plots for the levels of specific IgE to Bet v 1, Mal d 1, and Pru p 1 using ISAC, and also IgE levels to birch pollen and each fruit using ImmunoCAP to predict OAS, and calculated the area under the curve (AUC) as the performance of the classifier for each ROC curve. All statistical analyses were conducted with SPSS software (ver. 23.0; IBM Co., Armonk, NY) and *P*-values $< .05$ were considered significant.

3. Results

A total of 31 pediatric patients sensitized to birch pollen were included in this study (Table 1). The history of allergic disease and the results of allergy testing including CRD is presented in Supplement Tables, http://links.lww.com/MD/D913, http://links.lww.com/MD/D914. The study subjects were aged between 3 and 18 years (mean ± SD, 8.61 ± 2.81 years), and 67.7% (21/31) were males. Thirteen patients (13/31, 41.9%) were reported to have experienced OAS after eating an apple or peach and were diagnosed with OAS via positive skin-prick tests for at least one of the causative fruits. Among them, four patients reported acute urticaria after eating at least one plant-derived food, and one patient reported angioedema and acute urticaria on the whole body after eating a peach.

Table 2 shows the profiles of sensitization to Bet v 1, Bet v 2, and Bet v 4 in birch pollen-sensitized Korean children with allergic diseases. All patients (n = 13) with OAS were sensitized to Bet v 1. However, 61% of patients without OAS were sensitized to Bet v 1. The level of specific IgE to Bet v 1 was higher in patients with OAS than in those without OAS (median [interquartile range], 27.4 [16.5–45.6] vs 1.3 [0.0–3.0] kU/L, $P < .0001$; Fig. 1). The levels of specific IgE to Mal d 1 and Pru p 1, which are molecular components of apple and peach, respectively, were also higher in patients with OAS (18.9 [10.2–25.5] vs 1.3 [0.0–3.0] kU/L, $P < .0001$, and 9.8 [5.3–20.9] vs 1.3 [0.0–3.0] kU/L, $P < .0001$, respectively). To predict the presence of OAS by Bet v 1, Mal d 1, Pru p 1, and IgE levels for birch and each fruit using ImmunoCAP, the ROC curve showed high sensitivity and specificity (Fig. 2). A few patients were sensitized to Bet v 2 but all of those patients had OAS. The level of specific IgE to Bet v 2 was 0.00 [0.00–1.34] (median [interquartile range]) among patients with OAS and the results of CRD according to the presence of OAS is presented in Supplement Table 2.

Table 1

Demographic characteristics of the birch pollen-sensitized Korean children with allergic diseases enrolled in this study.

	Patients with OAS (n = 13)	Patients without OAS (n = 18)	*P*-value
Sex, males, %	84.6% (11/13)	55.6% (10/18)	.088
Age, years	7 (3–14)	8 (3–14)	.293
Total IgE, kU/L	548.1 (194.3–1434.0)	340.6 (30.5–3932.0)	.116
Specific IgE to birch pollen, kU/L	32.3 (3.4–88.4)	1.5 (0.0–37.0)	<.0001
Skin test IgE to birch pollen, A/H ratio	2.23 (1.50–4.53)	1.60 (0.00–2.50)	.011

Exception for proportions, data are presented as the medians with ranges in parentheses.
A/H ratio, ratio of diameter of allergen-induced wheal to that of histamine.
OAS = oral allergy syndrome.

Table 2

Percentage of birch-allergic patients with IgE reactivity to the recombinant allergens Bet v 1, Bet v 2, and Bet v 4.

Recombinant allergen	Patients with OAS (n = 13)	Patients without OAS (n = 18)	*P*-value	Total
Bet v 1	100% (13)	61% (11)	.011	77%
Bet v 2	31% (4)	0% (0)	n.a.	13%
Bet v 4	0% (0)	0% (0)	n.a.	0%

Data are presented as percentages with number of patients in parentheses.
OAS = oral allergy syndrome.

The patterns of sensitization to the PR-10 allergen family (including Bet v 1), profilin (including Bet v 2), and LTP were evaluated (Fig. 3). Approximately 69% (9/13) of patients with OAS were mono-sensitized to PR-10, and 31% (4/13) were poly-sensitized to profilin or LTP in addition to PR-10. One patient who was poly-sensitized to PR-10 and LTP and exhibited 1.05 IU of Pru p 3 had a history of peach-induced angioedema and urticarial rash on the whole body. Among patients without OAS, 67% (12/18) of patients without OAS were mono-sensitized to the PR-10 family, including eight patients sensitized to Bet v 1 and four patients sensitized to PR-10 allergens other than Bet v 1. And 33% (6/18) of patients without OAS were not sensitized to any of the allergen families.

4. Discussion

Birch pollen is not only major allergen in pollinosis but also one of main allergen related with OAS in many countries.[13–15] Because of such a relationship between birch pollen and OAS, birch pollen is almost only allergen which have been tried as allergen immunotherapy to treat OAS.[3,16,17] However, since CRD using microarray technology was introduced into the field of clinical allergy, it have been shown that there are heterogeneity of sensitization pattern based on CRD in birch pollen sensitized patients and also patients with OAS.[8–12] Birch pollen-sensitized Korean children with allergic diseases had unique patterns of sensitization to Bet v 1, Bet v 2, and Bet v 4 compared with a European population. Furthermore, sensitization profiles varied substantially according to the presence of OAS.

The profiles of IgE reactivity to three selected recombinant allergens (Bet v 1, Bet v 2, and Bet v 4) in birch pollen-sensitive patients varied among six different areas of Western Europe: Almost all Finnish, Swedish, and Austrian sera contained the IgE specific to Bet v 1 (≥98%). Bet v 1-specific IgE antibodies were found in 90% of the French sera, and in 65% and 62% of the sera from Switzerland and Italy, respectively.[11] This observation may be explained by sensitization to different allergen sources, which probably arose from different populations of birch trees.[9,18] Such differences could have an impact on allergen-specific prevention and therapeutic strategies in specific regions. Among birch pollen-sensitized Korean children with allergic diseases, sensitization to Bet v 1 was not as common (77%) as in those (90–100%) from Sweden, Finland, Austria, France, and Japan, but more common than reported from Switzerland and northern Italy.[15] Sensitization to Bet v 2 (13%) was not as common as in Sweden, and sensitization to Bet v 4 was rare in Korean children, similar to reports from the northern part of Japan.[15] Sensitization profiles to Bet v 1, Bet v 2, and Bet v 4 were markedly different according to the presence of OAS. Interestingly, sensitization rates to Bet v 1 among birch pollen-sensitized patients with OAS were as high as findings in Northern and Central Europe, whereas sensitization rates to Bet v 1 among

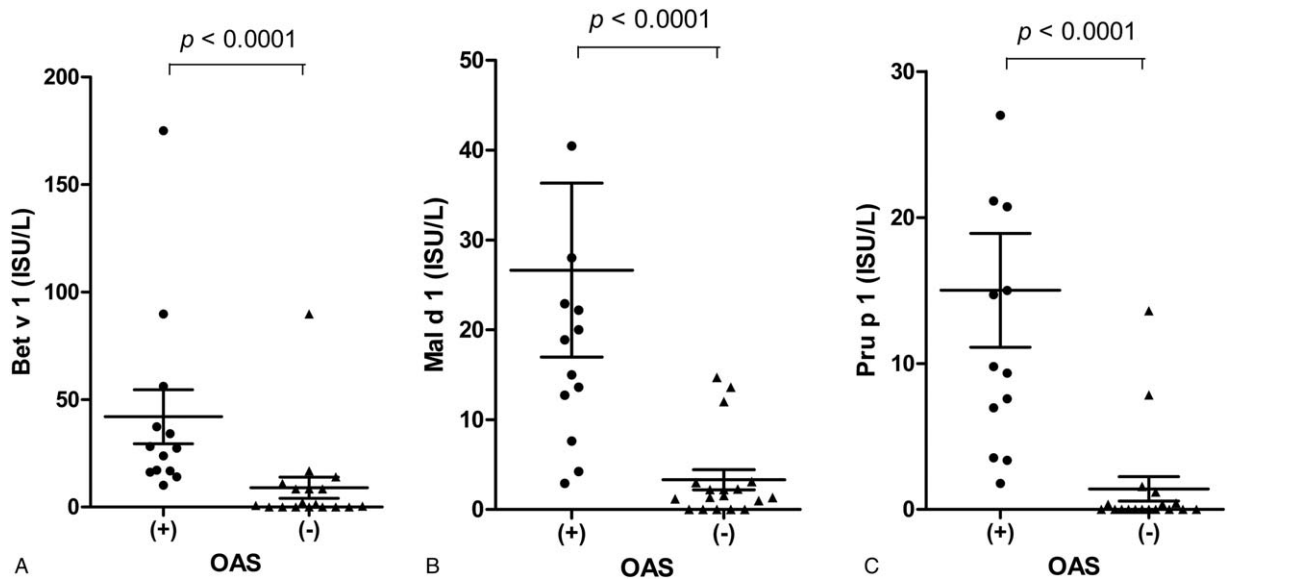

Figure 1. The levels of specific IgE to Bet v 1, Mal d 1, and Pru p 1 according to whether OAS was present (+) or absent (−). One outlier for Mal d 1 (137.8 ISU/L) and one outlier for Pru p 1 (54.2 ISU/L) among patients with OAS are not presented in the figure but the data were included in the statistical analysis for each allergen. The horizontal lines represent the means and error bars represent standard errors. IgE = immunoglobulin E, OAS = oral allergy syndrome.

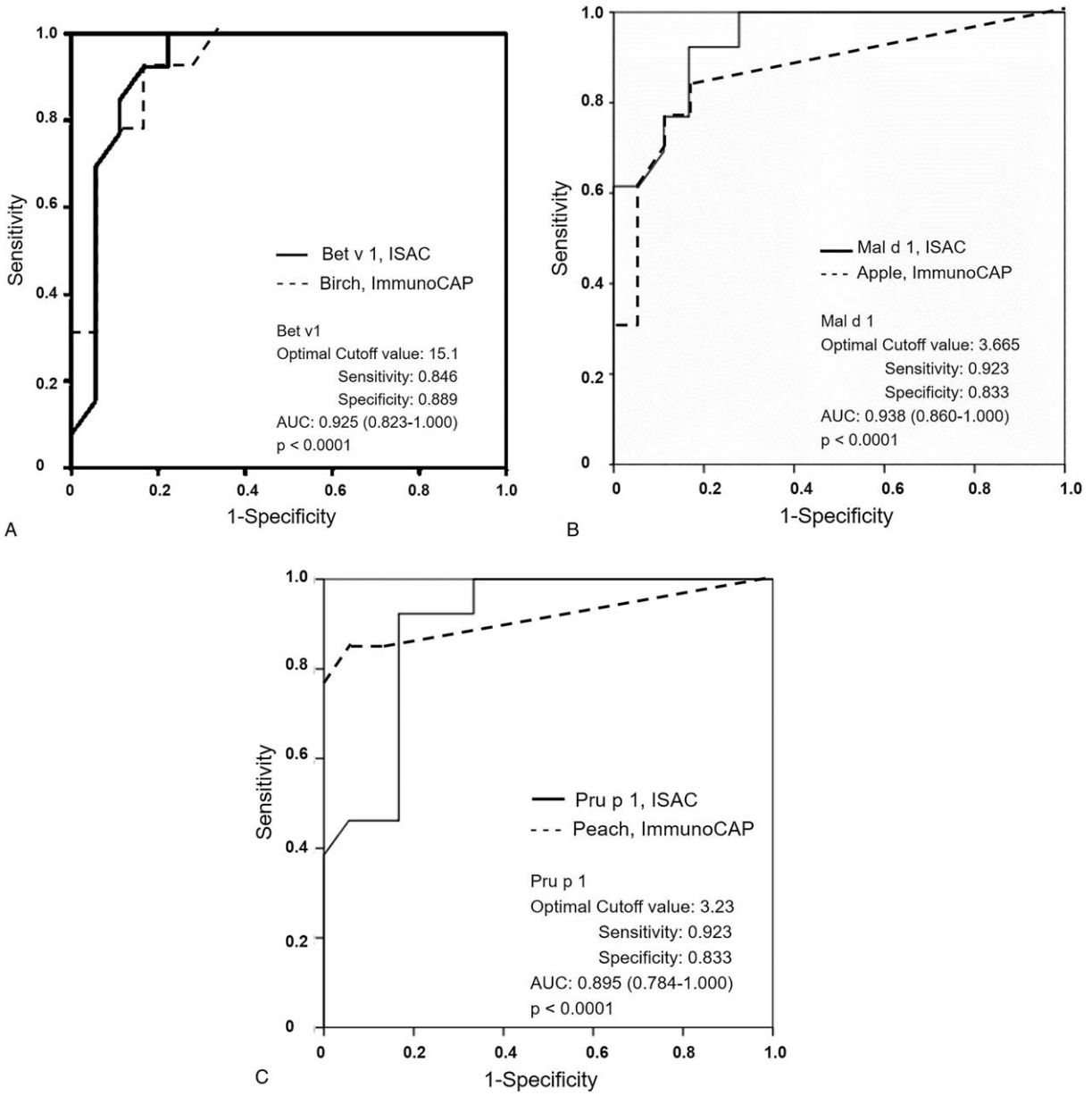

Figure 2. Receiver operating characteristic (ROC) curve to predict OAS. (A) ROC curve with the levels of specific IgE to Bet v 1 (ISAC) and birch pollen (ImmunoCAP), (B) ROC curve with the levels of specific IgE to Mal d 1 and apple, and (C) ROC curve with the levels of specific IgE to Pru p 1 and peach. IgE= immunoglobulin E.

those without OAS were as low as those reported from the western Mediterranean area. Although even many patients without OAS (61%) showed sensitization to Bet v 1, the titer of serum Ig E to Bet v 1 were much higher in patients with OAS (Figs. 1 and 2), which is in the line with previous report from Japan.[15] In addition, although the IgE reactivity to Bet v 2 has been reported to be various patients from region to region in birch pollen sensitized,[11,12] there have been no report about relationship between serum IgE to Bet v 2 (which belongs to profilin family) and OAS. However, it is consistent that multi-sensitization to profilin and PR-10 (including Bet v 1) is common in patients with OAS with previous reports in some other areas.[8,9]

More distinguishable differences between patients with and without OAS were observed in the sensitization patterns to the allergen families PR-10, LTP, and profilin. All birch pollen-sensitized Korean children with OAS were sensitized to PR-10, and 69% (9/13) of them were mono-sensitized to PR-10. The findings of this study are similar with the findings in Northern and Central Europe (Sweden, Denmark, Estonia, Lithuania, the Netherlands, and Switzerland), where monosensitization to PR-10 and, to a lesser degree, co-sensitization to profilin and PR-10, are dominant in patients with allergies to Rosaceae fruits,[9] and all of those patients are significantly associated with birch pollinosis.[9] By contrast, in the western Mediterranean area, allergies to Rosaceae fruits are caused by monosensitization to LTP or profilin, or co-sensitization to both of these allergens and such a near absence of PR-10 sensitization in the western Mediterranean area can probably be explained by a low

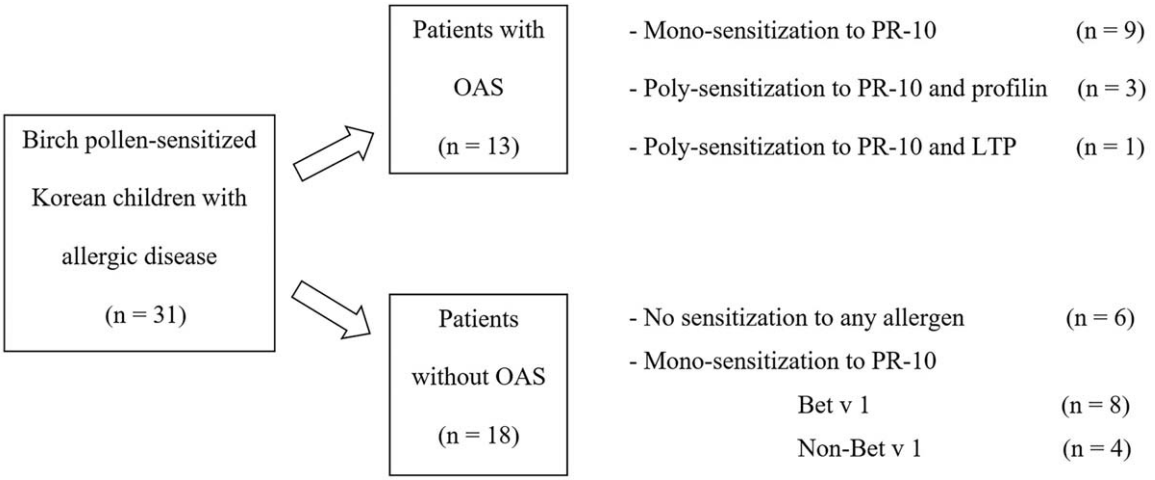

Figure 3. The profiles of IgE sensitization to the allergen families PR-10, LTP, and profilin in birch pollen-sensitized patients with and without OAS. IgE = immunoglobulin E, LTP = lipid transfer proteins, OAS = oral allergy syndrome, PR-10 = pathogenesis-related class 10 proteins.

distribution of birch trees.[9,18] Furthermore, Mastrorilli et al[8] suggested that differences in molecular endotyping of OAS could be related with clinical characteristics of pollinosis by reporting that IgE sensitization to all of three allergen families in Italian children with seasonal rhinitis was related with multimorbidity of allergic diseases, which is common in northern Italy.

Several important limitations of the present study should be mentioned. First, this study included a small number of patients; thus, a larger study is needed. However, this study suggests that there might be unique characteristics in the sensitization pattern related to birch pollen-sensitization among Korean children with allergic diseases compared with previous studies in Europe and Japan, which also included a small number of patients from each country. Second, the study population could have been different from those in European studies. Only children with allergic diseases and who were sensitized to birch pollen were enrolled and the causative fruits for OAS were apple or peach. The fruits that cause OAS could differ from region to region, but apple and peach were the most common fruits for OAS in Korea and have well-known cross-reactivity with birch pollen.

A fruit allergy can affect quality of life. As OAS is one of most common food allergies, defining the OAS molecular endotypes is important for developing treatments. This study showed a unique pattern of sensitization to birch pollen, a major allergen in pollinosis and OAS, and the allergen families among birch pollen-sensitized Korean children with allergic diseases. This study not only emphasized the needs to study molecular endotypes of birch pollen sensitized patient with allergic diseases according to specific region and the presence of OAS but also suggests that an approach based on specific regions and endotypes using CRD may be needed to develop an effective treatment strategy for pollinosis and related OAS.

Author contributions

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Methodology: Hey-Sung Baek.
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Writing – original draft: Jae-Woo Kwon.
Writing – review & editing: Hey-Sung Baek.

References

[1] Kang MG, Kim MY, Song WJ, et al. Patterns of inhalant allergen sensitization and geographical variation in Korean adults: a multicenter retrospective study. Allergy Asthma Immunol Res 2017;9:499–508.
[2] Haahtela T, Burbach GJ, Bachert C, et al. Clinical relevance is associated with allergen-specific wheal size in skin prick testing. Clin Exp Allergy 2014;44:407–16.
[3] Bucher X, Pichler WJ, Dahinden CA, et al. Effect of tree pollen specific, subcutaneous immunotherapy on the oral allergy syndrome to apple and hazelnut. Allergy 2004;59:1272–6.
[4] Breiteneder H, Ebner C. Molecular and biochemical classification of plant-derived food allergens. J Allergy Clin Immunol 2000;106:27–36.
[5] Kondo Y, Urisu A. Oral allergy syndrome. Allergol Int 2009;58:485–91.
[6] Kim MA, Kim DK, Yang HJ, et al. Pollen-food allergy syndrome in Korean pollinosis patients: a nationwide survey. Allergy Asthma Immunol Res 2018;10:648–61.
[7] Larenas-Linnemann D, Luna-Pech JA, Mosges R. Debates in allergy medicine: allergy skin testing cannot be replaced by molecular diagnosis in the near future. World Allergy Organ J 2017;10:32.
[8] Mastrorilli C, Tripodi S, Caffarelli C, et al. Endotypes of pollen-food syndrome in children with seasonal allergic rhinoconjunctivitis: a molecular classification. Allergy 2016;71:1181–91.
[9] Andersen MB, Hall S, Dragsted LO. Identification of European allergy patterns to the allergen families PR-10, LTP, and profilin from Rosaceae fruits. Clin Rev Allergy Immunol 2011;41:4–19.
[10] Rashid RS, Smith KA, Nambiar KZ, et al. Pollen-food syndrome is related to Bet v 1/PR-10 protein sensitisation, but not all patients have spring rhinitis. Allergy 2011;66:1391–2.
[11] Moverare R, Westritschnig K, Svensson M, et al. Different IgE reactivity profiles in birch pollen-sensitive patients from six European populations revealed by recombinant allergens: an imprint of local sensitization. Int Arch Allergy Immunol 2002;128:325–35.
[12] Rossi RE, Monasterolo G, Monasterolo S. Detection of specific IgE antibodies in the sera of patients allergic to birch pollen using recombinant allergens Bet v 1, Bet v 2, Bet v 4: evaluation of different IgE reactivity profiles. Allergy 2003;58:929–32.

[13] Choi WB, You JS, Yi YY, et al. Component-resolved diagnosis using microarray for diagnosing hypersensitivity to raw fruits in birch pollen sensitized children. Allergy Asthma Respir Dis 2015;3:200–5.
[14] Shirasaki H, Yamamoto T, Abe S, et al. Clinical benefit of component-resolved diagnosis in Japanese birch-allergic patients with a convincing history of apple or peach allergy. Auris Nasus Larynx 2017;44:442–6.
[15] Shirasaki H, Yamamoto T, Koyanagi Y, et al. Detection of specific IgE antibodies in sera of Japanese birch-allergic patients using recombinant allergens Bet v 1, Bet v 2 and Bet v 4. Allergol Int 2008;57:93–6.
[16] Pauli G, Larsen TH, Rak S, et al. Efficacy of recombinant birch pollen vaccine for the treatment of birch-allergic rhinoconjunctivitis. J Allergy Clin Immunol 2008;122:951–60.
[17] Kinaciyan T, Nagl B, Faustmann S, et al. Efficacy and safety of 4 months of sublingual immunotherapy with recombinant Mal d 1 and Bet v 1 in patients with birch pollen-related apple allergy. J Allergy Clin Immunol 2018;141:1002–8.
[18] Fernandez-Rivas M, van Ree R, Cuevas M. Allergy to Rosaceae fruits without related pollinosis. J Allergy Clin Immunol 1997;100:728–33.