

Sensitization profiles to peanut allergens across the United States



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ABSTRACT

Background: Measurement of IgE antibody to peanut components can aid in the prediction of allergic responses the food.

Objective: To investigate the association between patient demographics (age, location) and allergic sensitization to peanut components across the United States.

Methods: Serum samples from 12,155 individuals with peanut extract specific IgE levels of 0.35 kUA/L or higher were analyzed for IgE antibodies to Ara h 1, 2, 3, 8, and 9 by ImmunoCAP.

Results: Among this population of peanut sensitized individuals, 79.1% of children (<3 years old) were sensitized to one or more peanut storage proteins (Ara h 1, 2, and/or 3), in contrast to 64.2% of adolescents (12–15 years old) and 22.1% of adults (>20 years old). Although sensitization was more prevalent to Ara h 2 than to the other storage proteins, a sizable fraction of patients were sensitized to Ara h 1 and/or 3 but not to Ara h 2 (eg, 13% of children <3 years old). Moreover, 9.6% of children, 10.2% of adolescents, and 10.5% of adults were sensitized to Ara h 9, whereas 2.4% of children, 49.4% of adolescents, and 42.9% of adults produced IgE to Ara h 8 (pathogenesis-related protein 10). Sensitization to Ara h 8 alone was markedly higher in the Northeastern United States relative to other regions of the country.

Conclusion: We conclude that sensitization to individual peanut components is highly dependent on age and geographic location. Given that a severe allergic reaction to peanut is unlikely in individuals with isolated sensitization to Ara h 8, a sizable fraction of patients, in particular adolescents and adults, may be at lower risk than anticipated based only on demonstration of sensitization to whole peanut extract.

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Introduction

Peanut (*Arachis hypogaea*) has become one of the most popular and yet potent allergenic foods in the American diet. Whether eaten roasted or processed as peanut butter, peanut has caused an estimated 1.4% of children in the United States to manifest allergic symptoms that range from mild oral itching to fatal systemic anaphylaxis.^{1–5} Accurate diagnosis is vital to ensure that clinically allergic patients avoid peanut exposure. In contrast, overdiagnosis can result in an unnecessary anxiety and elimination of this healthy, protein packed, nutritious food from the diet.^{6,7} The diagnosis of peanut allergy begins with a thorough clinical history and evaluation of the patient's reaction temporally associated with peanut exposure.^{1–4,8–13} Sensitization

can be assessed by skin prick testing or specific IgE (sIgE) measurements to extracts of defatted peanut flour.^{8,9} A definitive diagnosis of peanut allergy can be obtained with a food challenge, which is largely performed at referral centers given it is a time- and labor-intensive process.^{8–12} In clinical practice, a diagnosis is often made through obtaining a convincing history of a reaction, in the setting of confirmed allergen sensitization, and oral food challenge may be deferred unless there is uncertainty in the history. Unfortunately, the diagnostic accuracy of both extract-based in vivo and in vitro sensitization tests is less than optimal, with a well-documented low clinical specificity. Thus, many positive peanut IgE antibody results are not associated with clinical reactivity.^{5,13–20}

An important recent development in peanut allergy diagnosis has been the availability of IgE antibody measurements to 5 carefully selected peanut allergen components (Ara h 1, 2, 3, 8, and 9).²⁰ Ara h 1 (7S globulin), Ara h 2 (2S albumin), and Ara h 3 (11S globulin) are highly abundant seed storage proteins, and IgE

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antibody responses to these structurally stable molecules have been associated with more severe systemic symptoms.^{15,21,22} Ara h 8 is a low-abundance protein that belongs to the pathogenesis-related protein 10 (PR-10) family and is susceptible to digestion and the extreme pH conditions in the stomach.²³ Thus, an isolated IgE response to Ara h 8 may potentially be associated with mild oral or no symptoms on intake of peanut. Ara h 9 belongs to the family of nonspecific lipid transfer proteins (nsLTPs).^{24,25} The clinical significance of Ara h 9 sensitization appears to be intermediate between that of sensitization to peanut storage proteins and Ara h 8.^{26–28}

Geographic differences in peanut sIgE responses to the available peanut components have been studied in different populations on 2 continents.²⁹ In New York and Stockholm, Sweden, sensitization to the storage proteins (eg, Ara h 1–3) was more common than in Madrid, Spain, where sensitization to Ara h 9 (nsLTP) was more prevalent. The Swedish participants had a higher sensitization rate to Ara h 8 than those in New York and Madrid. Little is known about how peanut component sensitization profiles vary across different regions of the United States. The aim of this study is to investigate the association between age and geographic location and the rates and pattern of sensitization to peanut extract and components in a large North American population tested for suspected peanut allergy.

Methods

Study Population

Deidentified serum samples from 16,123 consecutive patients were analyzed between March 1, 2015, and April 31, 2016, by Laboratory Corporation of America (LabCorp) following clinicians' referrals for a peanut allergen extract (f13) sIgE antibody measurement with automatic reflex of positive results to testing for sIgE to Ara h 1, 2, 3, 8, and 9. A total of 12,115 samples submitted for this testing produced f13 values of 0.35 kU_A/L or higher, triggering the reflex to components. The analytical IgE antibody data and demographic variables were retrieved from the core laboratory computerized database at LabCorp. No information on any patient's clinical reactivity to peanut was available for the samples tested. All analyses of deidentified serum specimens were performed under protocols approved by the Western Institutional Review Board.

Allergen sIgE Measurements

Peanut allergen sIgE antibody measurements were performed by ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden). Methods used included sIgE to peanut extract (f13) and components Ara h 1, Ara h 2, Ara h 3, Ara h 8, and Ara h 9. Analyses were performed in accordance with the manufacturer's instructions. Concentrations of IgE antibody of 0.35 kU_A/L or higher were arbitrarily defined as positive for the purposes of this analysis.

Statistical Analysis

Microsoft Excel was used to analyze data and produce the figures in this report.

Results

Patient Peanut sIgE Antibody Serologic Testing

Figure 1 depicts the patients' age distribution for all serum samples that tested positive (≥ 0.35 kU_A/L) for sIgE to Ara h 1, 2, 3, 8, and 9. The frequency of positive test results for Ara h 1, 2, and 3 was maximal in the group of 3- to 9-year-old children, and it decreased with increasing age. In contrast, the presence of Ara h 8 (PR-10) sIgE increased from 2.4% at 0 to 3 years of age to 49.5% at 15 to 20 years

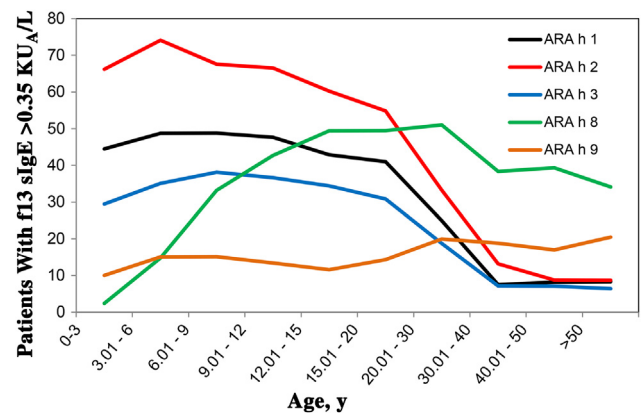


Figure 1. Age dependency of component sensitization (≥ 0.35 kU_A/L) for all reflexed serum samples that were tested for IgE to Ara h 1, 2, 3, 8, and 9. f13 indicates the peanut allergen extract; sIgE, specific IgE.

of age. The patterns of component sensitization for different age intervals and the entire population are described in eTable 1.

Regional Variation of Sensitization to Peanut in the United States

Table 1 lists regional rates of positivity (≥ 0.35 kU_A/L) across the age groups for IgE antibodies specific for Ara h 2; one or more of Ara h 1, 2, and 3; Ara h 8 (PR-10), and Ara h 9 (nsLTP). The data are tabulated by regions of the United States (Northeast [$n = 4529$], South [$n = 6025$], Midwest [$n = 586$], and West [$n = 888$]) as defined by the United States Census Bureau.³⁰ A 2-way analysis of variance of these percentages showed highly significant differences ($P < .001$) attributable to age and region. Ara h 8 showed a unique regional trend, with a much higher frequency in the Northeast United States than in the other regions. This finding presumably reflects a more intense exposure to pollen of tree species, such as birch, which contain major allergens belonging to the PR-10 protein family. Analysis of birch pollen sIgE results produced during a 2-year period by LabCorp ($n = 330,489$) revealed the following sensitization (≥ 0.35 kU_A/L) pattern: Northeast, 20.4%; South, 14.3%; Midwest, 11.2%; and West, 14.3%.

IgE Binding to Determinants Other Than Ara h 1, 2, 3, 8, and 9

Of the 12,155 individuals with positive IgE results to peanut (≥ 0.35 kU_A/L), 17.1% had sIgE levels less than 0.35 kU_A/L for all 5 available peanut components. More than half (54.4%) of individuals with f13 sIgE values between 0.35 and 1.00 kU_A/L ($n = 2281$) had all component sIgE levels less than 0.35 kU_A/L. Nearly one-third (32.7%) of individuals with f13 sIgE values between 0.35 and 1.00 kU_A/L had values below the limit of detection (0.1 kU_A/L) for all 5 available peanut components. Of the 5,511 individuals with f13 sIgE values between 1.01 and 15.0 kU_A/L, 14.8% had all component sIgE levels less than 0.35 kU_A/L. Of the 4,363 individuals with f13 sIgE values greater than 15 kU_A/L, 0.5% had all component sIgE levels less than 0.35 kU_A/L. Figure 2 shows that the frequency of these cases increased with age and was lower in the Northeast region than in the other regions of the country ($P < .001$).

Discussion

Peanut extracts used in in vivo and in vitro diagnostic testing contain a heterogeneous mixture of extractable allergenic proteins in different proportions, some of which are serologically highly specific to peanut, whereas many are related to and are homologous with other plant-based proteins, such as pollen allergens, thus capable of eliciting cross-reactivity. IgE antibody binding to a

Table 1
Regional Rates of Positivity for Peanut Components by Age

Component	Positivity rate by age range in years, %										
	Combined	0.00–3.00	3.01–6.00	6.01–9.00	9.01–12.00	12.01–15.00	15.01–20.00	20.01–30.00	30.01–40.00	40.01–50.00	>50.00
West											
Ara h 1	38.6	42.9	48.8	44.9	45.9	31.5	28.9	27.7	7.7	5.6	3.6
Ara h 2	57.1	66.4	76.7	62.0	66.2	49.4	44.6	27.7	15.4	5.6	3.6
Ara h 3	28.3	26.1	32.6	38.0	37.8	20.2	18.1	21.3	7.7	11.1	3.6
Ara h 8	16.0	0.8	5.2	15.2	20.3	23.6	32.5	23.4	26.9	16.7	32.1
Ara h 9	17.8	7.6	18.0	20.3	18.9	19.1	16.9	27.7	23.1	16.7	17.9
Midwest											
Ara h 1	48.5	40.2	52.2	60.8	64.8	50.0	45.7	23.3	6.7	<1.0	8.3
Ara h 2	70.5	71.7	84.1	82.5	85.2	62.1	56.5	33.3	13.3	<1.0	16.7
Ara h 3	35.3	28.3	37.0	44.3	47.7	43.1	28.3	13.3	6.7	<1.0	16.7
Ara h 8	21.0	2.2	13.8	22.7	37.5	24.1	41.3	20.0	20.0	30.0	16.7
Ara h 9	14.7	12.0	16.7	13.4	13.6	10.3	15.2	23.3	26.7	20.0	8.3
South											
Ara h 1	41.4	43.8	47.0	47.1	44.6	40.4	38.8	23.0	7.6	9.3	10.3
Ara h 2	59.7	65.1	72.5	66.3	62.7	55.8	54.0	33.5	12.5	9.3	8.9
Ara h 3	31.0	28.9	34.5	36.3	34.1	31.9	31.0	16.7	7.6	7.0	6.8
Ara h 8	25.7	2.3	11.8	26.7	36.3	44.5	40.3	44.5	28.5	24.4	24.7
Ara h 9	14.3	10.0	16.0	15.2	14.2	11.8	14.5	16.7	17.4	15.1	25.3
Northeast											
Ara h 1	46.1	46.5	50.5	51.5	50.2	47.8	45.9	26.2	7.8	8.7	6.8
Ara h 2	64.3	67.0	74.1	70.0	69.8	68.1	58.2	34.4	14.3	10.1	9.5
Ara h 3	34.7	31.2	35.8	40.9	38.5	39.6	33.6	20.8	6.5	7.2	5.4
Ara h 8 ^a	42.8	2.7	20.5	45.6	54.9	62.1	63.7	67.0	61.0	65.2	54.1
Ara h 9	12.8	10.2	13.1	13.8	11.1	10.1	14.0	19.9	19.5	18.8	14.9

^aAra h 8 in the Northeast region was significantly higher than in other regions.

peanut extract can therefore reflect a primary peanut sensitization or a cross-reactive pollen sensitization or a combination of both. As a result, natural peanut extract is not always diagnostically specific for peanut allergy.^{1,3,15–17,31–34} Component-resolved diagnostics have been shown by multiple studies to potentially complement peanut extract testing by measuring sensitization to peanut proteins of particular clinical relevance.^{31–35} This report presents unique demographic and geographic information about the sensitization profiles of Americans who are being evaluated for suspected peanut allergy.

Ara h 2 sensitization was more prevalent ($P < .05$) than sensitization to Ara h 1 or Ara h 3, with 61.5% of peanut extract sIgE positive (≥ 0.35 kU_A/L) samples being positive for IgE antibodies to Ara h 2. Of patients who tested positive to peanut extract, 41.4% were Ara h 2 positive and cosensitized to Ara h 1 and/or 3. Importantly, 5.2% of peanut extract sIgE positive serum samples were positive for Ara h 1 and/or 3 and negative for Ara h 2, which emphasizes the potential utility of measuring IgE

antibody to all 3 storage proteins in a diagnostic evaluation. This finding is more pertinent for infants (0–3 years of age) who tested positive to peanut extract, with 12.6% testing Ara h 2 negative and Ara h 1 and/or Ara h 3 positive.

The progressive decline in sensitization to the storage proteins with age, which reached only 10% of adults older than 30 years, may reflect a dilution of individuals with a primary peanut sensitization by ones with pollen sensitization, which gives rise to serologic cross-reactivity with peanut. An alternative explanation would be a frequent loss of peanut storage protein sensitization over time. This possibility cannot be excluded but would require a sizable longitudinal study to be accurately assessed.

In the present study, Ara h 8 positivity was relatively low for young children and increased with age for adolescents and young adults. The dependency on age observed in the current study population is consistent with the expectation that increased exposure to pollen occurs as an individual matures. Considering the data on Ara h 8 monosensitization presented here, a sizable fraction of individuals investigated for a suspected peanut allergy, in particular adolescents and adults, appear to not have a primary peanut sensitization.

IgE positivity to Ara h 9 affected 10% to 20% of the US population, regardless of age. Ara h 9 belongs to the nsLTPs that form a part of the prolamin superfamily and is cross-reactive with homologous proteins in a variety of Rosaceae fruits.^{24,25} Clinical studies have found that the assessment of an isolated IgE response to Ara h 9 must be interpreted within the context of the patient's clinical history.¹⁵ If there is no patient history of clinical symptoms to peanut, then the risk of a severe allergic reaction is low. It has been suggested that, in the presence of clinical symptoms, Ara h 9 sensitized patients should be managed with the same precautions as individuals with confirmed peanut allergy.¹⁵

Peer-reviewed data in the literature support the conclusion that IgE antibody specific for the abundant and stable peanut storage protein Ara h 2 in particular enhances diagnostic specificity.^{5,20,22,31,34–39} IgE to Ara h 2 above certain levels may be useful in discriminating between peanut allergic and tolerant individuals. The first allergic reactions to peanut typically occur before the age of 2 years and seldom after the age of 17 years.^{40–43} Infants and

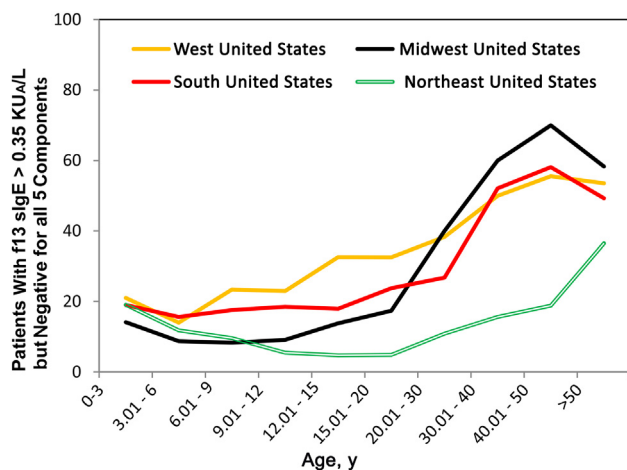


Figure 2. Percent of peanut allergen extract (f13)-positive samples negative for all 5 components by patient age and geographic region. sIgE indicates specific IgE.

young children with eczema and sensitization to peanut predominantly recognize the storage proteins, even before the introduction of peanut into their diet.^{44,45} This clinical pattern correlates strongly with the age dependency of sensitization to peanut storage proteins, as was also observed in our cohort.

Certain geographic variations in peanut component sensitization have been documented. Americans in New York were more frequently sensitized to Ara h 1, Ara h 2, and Ara h 3, whereas individuals in Spain and Sweden were more frequently sensitized to Ara h 9 and Ara h 8, respectively.^{29,42} Ara h 9 has been implicated as an important predictor of clinical peanut allergy in the Spanish and Asian populations but not in others.^{25,46} Heterogeneity in the clinical and immunologic phenotype of peanut allergy in distinct geographic areas likely reflects exposure to different pollen and variance in local dietary traditions.³¹ Comparison of patterns of age-dependent sensitization to peanut components in our data set revealed clear regional differences. Sensitization to Ara h 1, 2, 3, and 9 were relatively consistent across the country. Analysis of simultaneous 95% confidence intervals revealed that Ara h 8 sensitization in the Northeast United States was consistently higher than the in other 3 regions of the United States. This regional disparity correlates with the finding that birch pollen sIgE sensitization was higher in the Northeast than in other regions of the United States.

Epidemiologic studies have suggested that high rates of sensitization to peanut extract in nonselected cohorts of adolescents and adults is, to a large extent, caused by cross-reactivity to pollen.^{47,48} Although approximately 50% of adolescents and young adults in our study were sensitized to birch pollen related Ara h 8 (Fig 1), more than 60% were sensitized to one or more of the seed storage proteins. Among the younger children, up to 80% were sensitized to seed storage proteins and a much lower percentage to Ara h 8. The age dependency of Ara h 8 sensitization is similar to that observed for airborne allergens by puncture skin test results reported in the National Health and Nutrition Examination Surveys II and III.⁴⁹

We conclude that sensitization to peanut storage proteins (Ara h 1, 2, and 3) is more common in children than in adult individuals being evaluated for suspected peanut allergy, whereas the opposite is true for the Bet v 1-related PR-10 peanut protein Ara h 8. Although Ara h 2 sensitization predominates among the seed storage proteins, a significant number of seed storage protein sensitized individuals would be missed if Ara h 1 and 3 were not also assessed, especially in young children. Sensitization to the lipid transfer protein Ara h 9 occurs at a modest prevalence and appears not to be related to age or geographic region. However, additional data and more robust research studies are needed to better define the clinical utility of peanut component testing and how incorporation of these next-generation tests can better inform clinical decision making for the diagnosis of peanut allergy. To our knowledge, this study provides the first widespread detailed assessment of the variation of sensitization patterns to peanut across the United States, which is an important step toward better understanding of how to optimize the diagnostic utility of this testing modality.

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Supplementary Data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.anai.2017.06.021>.

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Supplementary Data

Table 1
Sensitization to Combinations of Components by Patient Age

Component	No. (%) of patients by age range, y							
	0.00–3.00 (n = 1,704)	3.01–6.00 (n = 2,285)	6.01–9.00 (n = 2,285)	9.01–12.00 (n = 2,081)	12.01–15.00 (n = 1,368)	15.01–20.00 (n = 1,202)	>20.00 (n = 1,230)	Combined (n = 12,155)
Ara h 1 >0.35	758 (44.5)	1,114 (48.8)	1,115 (48.8)	992 (47.7)	587 (42.9)	493 (41.0)	186 (15.1)	5,245 (43.2)
Ara h 2 >0.35	1,128 (66.2)	1,693 (74.1)	1,544 (67.6)	1,384 (66.5)	824 (60.2)	659 (54.8)	246 (20.0)	7,478 (61.5)
Ara h 3 >0.35	502 (29.5)	802 (35.1)	871 (38.1)	763 (36.7)	471 (34.4)	371 (30.9)	146 (11.9)	3,926 (32.3)
Ara h 8 >0.35	34 (2.4)	256 (14.8)	499 (33.2)	568 (42.7)	396 (49.4)	317 (49.5)	109 (42.9)	2,179 (31.5)
Ara h 9 >0.35	151 (9.6)	282 (13.7)	254 (13.0)	207 (12.2)	119 (10.2)	129 (12.4)	65 (10.5)	1,207 (11.9)
Only Ara h 1 >0.35	107 (6.0)	54 (1.8)	36 (1.1)	38 (1.1)	24 (1.2)	20 (0.6)	13 (0.5)	292 (1.8)
Only Ara h 2 >0.35	492 (27.8)	628 (22.7)	440 (11.6)	403 (10.1)	242 (8.2)	174 (7.0)	67 (2.4)	2,446 (13.9)
Only Ara h 3 >0.35	49 (2.3)	49 (1.4)	32 (0.8)	11 (0.2)	26 (1.1)	17 (0.9)	10 (0.5)	194 (1.0)
Only Ara h 8 >0.35	5 (0.3)	71 (3.1)	224 (9.8)	285 (13.7)	262 (19.2)	260 (21.6)	357 (29.0)	1,464 (12.0)
Only Ara h 9 >0.35	18 (1.1)	51 (2.2)	56 (2.5)	36 (1.7)	21 (1.5)	25 (2.1)	111 (9.0)	318 (2.6)
Any of Ara h 1, 2, or 3 >0.35	1,348 (79.1)	1,840 (80.5)	1,631 (71.4)	1,445 (69.4)	878 (64.2)	699 (58.2)	272 (22.1)	8,113 (66.7)
Ara h 1, 2, and 3 >0.35	340 (20.0)	660 (28.9)	776 (34.0)	701 (33.7)	418 (30.6)	336 (28.0)	124 (10.1)	3,355 (27.6)
Ara h 1 and 2 >0.35 with Ara h 3 <0.35	247 (14.5)	356 (15.6)	284 (12.4)	241 (11.6)	141 (10.3)	134 (11.1)	46 (3.7)	1,449 (11.9)
Ara h 1 and 3 >0.35 with Ara h 2 <0.35	64 (3.8)	44 (1.9)	19 (0.8)	12 (0.6)	4 (0.3)	3 (0.2)	3 (0.2)	149 (1.2)
Ara h 2 and 3 >0.35 with Ara h 1 <0.35	49 (2.9)	49 (2.1)	44 (1.9)	39 (1.9)	23 (1.7)	15 (1.2)	9 (0.7)	228 (1.9)
None of Ara h 1, 2, and 3 >0.35	356 (20.9)	445 (19.5)	654 (28.6)	636 (30.6)	490 (35.8)	503 (41.8)	958 (77.9)	4,042 (33.3)
Any of Ara h 1, 2, or 3 >0.35 and Ara h 8 9 not >0.35	1,183 (69.4)	1,377 (60.3)	991 (43.4)	784 (37.7)	448 (32.7)	343 (28.5)	142 (11.5)	5,268 (43.3)
Any of Ara h 1, 2, or 3 and Ara h 8 >0.35	14 (0.8)	181 (7.9)	386 (16.9)	454 (21.8)	311 (22.7)	227 (18.9)	65 (5.3)	1,638 (13.5)
Any of Ara h 1, 2, or 3 and Ara h 9 >0.35	131 (7.7)	207 (9.1)	141 (6.2)	93 (4.5)	34 (2.5)	39 (3.2)	21 (1.7)	666 (5.5)
Any of Ara h 1, 2, or 3 and Ara h 8 and 9 >0.35	20 (1.2)	75 (3.3)	113 (4.9)	114 (5.5)	85 (6.2)	90 (7.5)	44 (3.6)	541 (4.5)
Any of Ara h 1, 2, 3, 8, or 9 >0.35	1,373 (80.6)	1,973 (86.3)	1,947 (85.2)	1,802 (86.6)	1,179 (86.2)	1,002 (83.4)	802 (65.2)	10,078 (82.9)
None of Ara h 1, 2, or 3 >0.35 and Ara h 8 and 9 >0.35	2 (0.1)	11 (0.5)	36 (1.6)	36 (1.7)	18 (1.3)	18 (1.5)	62 (5.0)	183 (1.5)
None of Ara h 1, 2, 3, 8, or 9 >0.35	331 (19.4)	312 (13.7)	338 (14.8)	279 (13.4)	189 (13.8)	200 (16.6)	428 (34.8)	2,077 (17.1)