The First Clinical Study of Ara h 6 Relevance in a Pediatric Peanut Allergy Population in the United States (US).

J.M. Palmieri, D.O.[a,b], S. Anvari, M.D., M.S.[a,b,c] , I.K. Chinn, M.D[a,b,c] , N. Fernandez-Davila, M.D[a,b], L. Forbes, M.D[a,b,c] , M. Gupta, M.D[a,b,c] , J. Hajjar, M.D[a,b,c] , L. Lyter-Reed, APRN[a,b,c] , L. Noroski, M.D[a,b,c], A Reiland, APRN[a,b,c] F. Seeborg, M.D[a,b,c] , B. Getts, PhD[d], P. Kearney, PhD[d], H. Butler[d], C. M. Davis, M.D.[a,b,c]

a)Division of Immunology, Allergy, and Retrovirology, Texas Children's Hospital, Houston, TX, b) Department of Pediatrics, Baylor College of Medicine, Houston, TX, c) William T. Shearer Center for Human Immunobiology, Texas Children's Hospital, Houston, TX, d) AllerGenis LLC.

Introduction

Peanut allergy (PA) accounts for 25% of children with food allergy and often persists throughout life, however diagnostic testing has poor positive predictive accuracy leading to 60% over-diagnosis. Peanut components, especially Ara h 1, 2, and 3, are used to augment diagnostics but accuracy remains lacking.

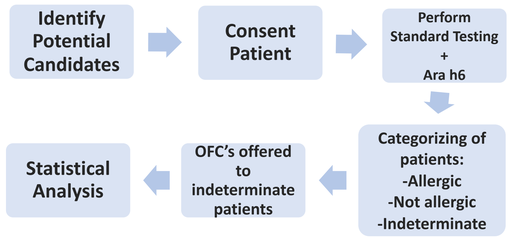
There is growing interest in the diagnostic potential of the peanut component Ara h 6 due in part to Ara h 2 and 6 sharing 60% sequence identify and multiple epitopes. European data shows differing associations based on geographic location with Ara h 6 and either Ara 2 or Ara h 9. Additionally, there are reports of Ara h 6 mono-sensitized oral food challenge positive peanut allergic patients. We present the first US study evaluating the diagnostic utility of Ara h 6. We hypothesize that Ara h 6 will correlate strongly with Ara h 2 in our patient population.

Objectives

- Examine the Ara h 6 association with peanut sIgE and Ara h 1, 2, 3, 8, and 9 in our population.
- Evaluate utility of Ara h 6 in peanut allergy diagnosis in an ethnically diverse pediatric peanut allergic population

Methodology

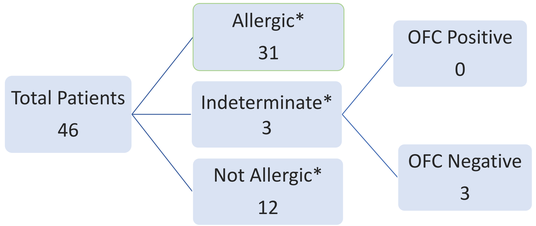
Figure 1: Overall study process



- Standard testing: sIgE with peanut components and SPT
- 95% PPV:
  SPT ≥ 8 mm (≥ 3mm if under 2 years old), sIgE ≥ 15 kU/L
- Values considered negative:
  SPT < 3mm or sIgE ≤0.1 kUA/L
- Oral food challenges offered to all indeterminate category patients.
- Cohorts were compared using independent, two-sample t-tests and Wilcoxon rank sum tests.
- Values below the limit of detection (<0.10) were assigned a value of 0.09
- Values above the limit of detection (>100) were assigned a value of 100.1.

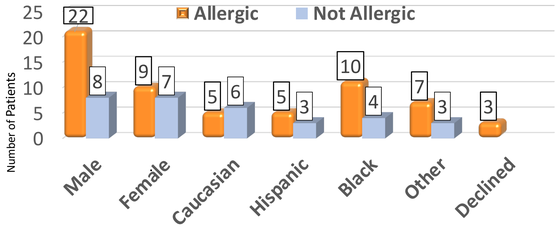
Patient Demographics

Figure 2: Categorization of patients.



*Based on standard testing
** Study is ongoing, 71 patients currently enrolled

Figure 3: Ethnicity, sex, and allergic status*



Ara h Component Distribution, Sensitivity, and Specificity

Table 1: Overall Summary Statistics

Overall Summary Statistics			
Variable	Level*	Summary Statistic	Dominant component percentage+**
sIgE	Mean (sd)	32.6 (37.4)	NA
	Median (p_{25}, p_{75})	20.8 (0.1, 54.0)	
	Median (min, max)	20.8 (0.1, 100.1)	
Ara h 1	Mean (sd)	16.9 (30.0)	19%
	Median (p_{25}, p_{75})	0.8 (0.1, 24.2)	
	Median (min, max)	0.8 (0.1, 100.1)	
Ara h 2	Mean (sd)	29.0 (36.6)	**48%**
	Median (p_{25}, p_{75})	12.0 (0.1-51.3)	
	Median (min, max)	12.0 (0.1-100.1)	
Ara h 3	Mean (sd)	9.1 (23.2)	0%
	Median (p_{25}, p_{75})	0.3 (0.1, 1.7)	
	Median (min, max)	0.3 (0.1, 100.1)	
Ara h 6	Mean (sd)	23.1 (32.6)	**23%**
	Median (p_{25}, p_{75})	7.2 (0.1, 40.2)	
	Median (min, max)	7.2 (0.1, 100.1)	
Ara h 8	Mean (sd)	2.7 (9.5)	0%
	Median (p_{25}, p_{75})	0.1 (0.1, 0.1)	
	Median (min, max)	0.1 (0.1, 54.0)	
Ara h 9	Mean (sd)	1.3 (3.6)	0%
	Median (p_{25}, p_{75})	0.1 (0.1, 0.3)	
	Median (min, max)	0.1 (0.1, 20.3)	

+Bolded numbers indicate the two dominant components

*Summary statistics were reported by median p25/p75 and minimum/maximum as artificial values were substituted for values below and above limits of detection (see methodology) and data was rightward skewed.

**3 patients (9.6%) did not have a dominant component as Ara h 1, 2, and 6 were all >100

Figure 4: Distribution of component by type and cohort

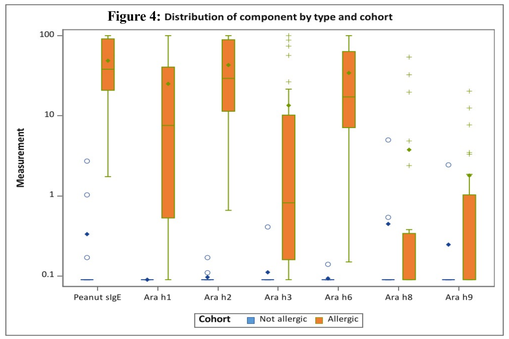


Table 2: Component sensitivity and specificity*

Measure	Statistic	Estimate (standard error)	95% Confidence Limit (lower/upper)
sIgE	Sens.	**0.94** (0.04)	0.85/1.00
	Spec.	**1.0** (0.00)	1.00/1.00
Ara h 1	Sens.	0.87 (0.60)	0.75/0.99
	Spec.	1.0 (0.00)	1.00/1.00
Ara h 2	Sens.	**1.0** (0.00)	1.00/1.00
	Spec.	**1.0** (0.00)	1.00/1.00
Ara h 3	Sens.	0.77 (0.08)	0.63/0.92
	Spec.	0.93 (0.06)	0.81/1.00
Ara h 6	Sens.	**0.97** (0.03)	0.91/1.00
	Spec.	**1.0** (0.00)	1.00/1.00
Ara h 8	Sens.	0.32 (0.08)	0.16/0.49
	Spec.	0.87 (0.09)	0.70/1.00
Ara h 9	Sens.	0.49 (0.09)	0.31/0.66
	Spec.	0.93 (0.06)	0.81/1.00

* Bolded values indicate measures with the highest sensitivity and specificity

Component Correlations

Table 3: Spearman rank correlation coefficients estimating the correlation between the seven outcome measures*

Spearman Correlation Coefficients							
	sIgE	Ara h 1	Ara h 2	Ara h 3	Ara h 6	Ara h 8	Ara h 9
sIgE	1	0.81	0.97	0.89	0.95	0.31	0.58
		<0.0001	<0.0001	<0.0001	<0.0001	0.041	<0.0001
Ara h 1	0.81	1	0.77	0.79	0.82	0.35	0.53
	<0.0001		<0.0001	<0.0001	<0.0001	0.0175	0.0002
Ara h 2	0.97	0.77	1	0.85	0.96	0.28	0.54
	<0.0001	<0.0001		<0.0001	<0.0001	0.06	<0.0001
Ara h 3	0.89	0.79	0.85	1	0.86	0.3	0.7
	<0.0001	<0.0001	<0.0001		<0.0001	0.04	<0.0001
Ara h 6	0.95	**0.82**	**0.96**	**0.86**	1	0.26	**0.59**
	<0.0001	<0.0001	<0.0001	<0.0001		0.08	<0.0001
Ara h 8	0.31	0.35	0.28	0.3	0.26	1	0.38
	0.04	0.02	0.06	0.04	0.08		0.01
Ara h 9	0.58	0.53	0.54	0.7	0.59	0.38	1
	<0.0001	0.0002	<0.0001	<0.0001	<0.0001	0.01	

* Ara h 6 significant correlations are bolded

Conclusion and Discussion

- Ara h 6 was the dominant component in 23% of peanut allergic (PA) patients in our population.
- Ara h 6 showed the greatest correlation with Ara h 2 but a strong correlation with Ara 1 and Ara h 3 was also found.
- A moderate correlation with Ara h 6 and Ara h 9 was noted as well.
- Ara h 2 remains more sensitive than Ara h 6 for PA diagnosis
- One Ara h 6 mono-sensitized patient was found
- Ara h 6 is a relevant component in the US pediatric population.

References

Gupta RS, Springston EE, Warrier MR The prevalence, severity, and distribution of childhood food allergy in the United States. Pediatrics. 2011;128(1):e9-17.

Sicherer SH, Wood RA. Advances in diagnosing peanut allergy. J Allergy Clin Immunol Pract. 2013;1(1):1-13.

Bird JA, Crain M, Varshney P. Food allergen panel testing often results in misdiagnosis of food allergy. The Journal of Pediatrics. 2015;166(1):97–100.

Keet CA, Johnson K, Savage JH, Hamilton RG, Wood RA. Evaluation of Ara h2 IgE thresholds in the diagnosis of peanut allergy in a clinical population. The Journal of allergy and clinical immunology Pract. 2013;1(1):101-103.

Hemmings, O., Du Toit, G., Radulovic, S., Lack, G., Santos, A.,*Ara h 2 is the dominant peanut allergen despite similarities with Ara h 6*, Journal of Allergy and Clinical Immunology,Volume 146 (3); 2020, 621-630

Tontini, C., Marinangeli L., Maiello N., Abbadessa S., Villalta, D., Antonicelli. L., *Ara h 6 sensitization in peanut allergy: friend, foe or innocent bystander?*, Eur Ann Allergy Clin Immunol; Volume 49;18-21