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Investigation of Increased *TPSAB1* Copy Number as a Biomarker of Food Allergy Reaction Severity

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- Midwest Allergy Research Institute (MARI) Food Allergy Pilot Research Award

Poll Question

What is the best marker of food allergy severity you use in clinical practice?

a. Skin prick test wheal size
b. Whole specific IgE
c. Component-resolved specific IgE
d. History of previous reaction severity
e. Other
f. No reliable predictors

Background

Epidemiology of Food Allergy

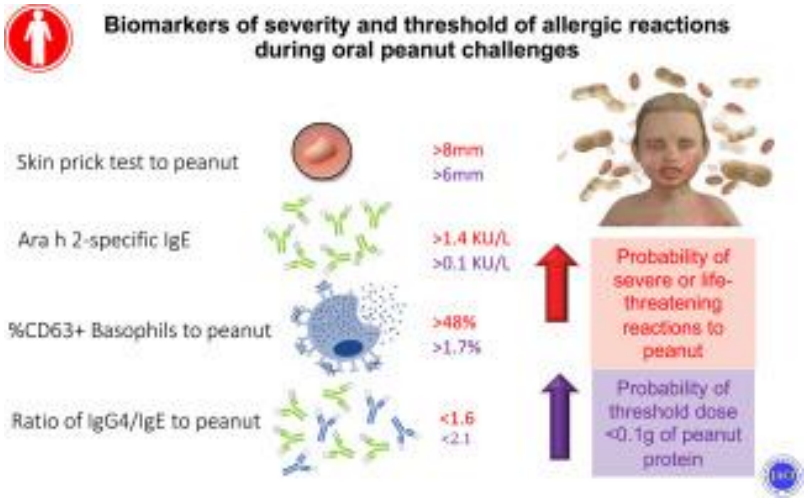
- Prevalence and incidence of food allergy continues to rise in both adults and children
- Fatal anaphylaxis attributable to food is rare
- Unpredictability of reaction severity creates stress and affects quality of life for patients with food allergies

Sicherer SH, Sampson HA. JACI 2018.
Umasunthar T et al. *Clin Exp Allergy,*2013.
Antolin-Amerigo et al. *Clin Mol Allergy*, 2016
Turner PJ etal. *Allergy*, 2016.

Background

Predictors of Severity

- Specific IgE (sIgE) testing to food allergen components
- Basophil activation testing (BAT)
- Epitope testing



- Limitations
  - Interpretation of component testing results varies by age and geographic region and not available for all foods
  - BAT not routinely performed in commercial laboratories & potential issues with sample stability

Santos, Alexandra F. et al. Biomarkers of severity and threshold of allergic reactions during oral peanut challenges. J Allergy Clin Immunol, 2020. 146(2): 344 – 355.
Valcour et al. Sensitization profiles to peanut allergens across the United States. Ann Allergy Asthma Immunol, 2017. 119(3)262-266.e1.
Santos AF …. Lack G. Biomarkers of severity and threshold of allergic reactions during oral peanut challenges. J Allergy Clin Immunol. 2020 Aug;146(2):344-355.

Background

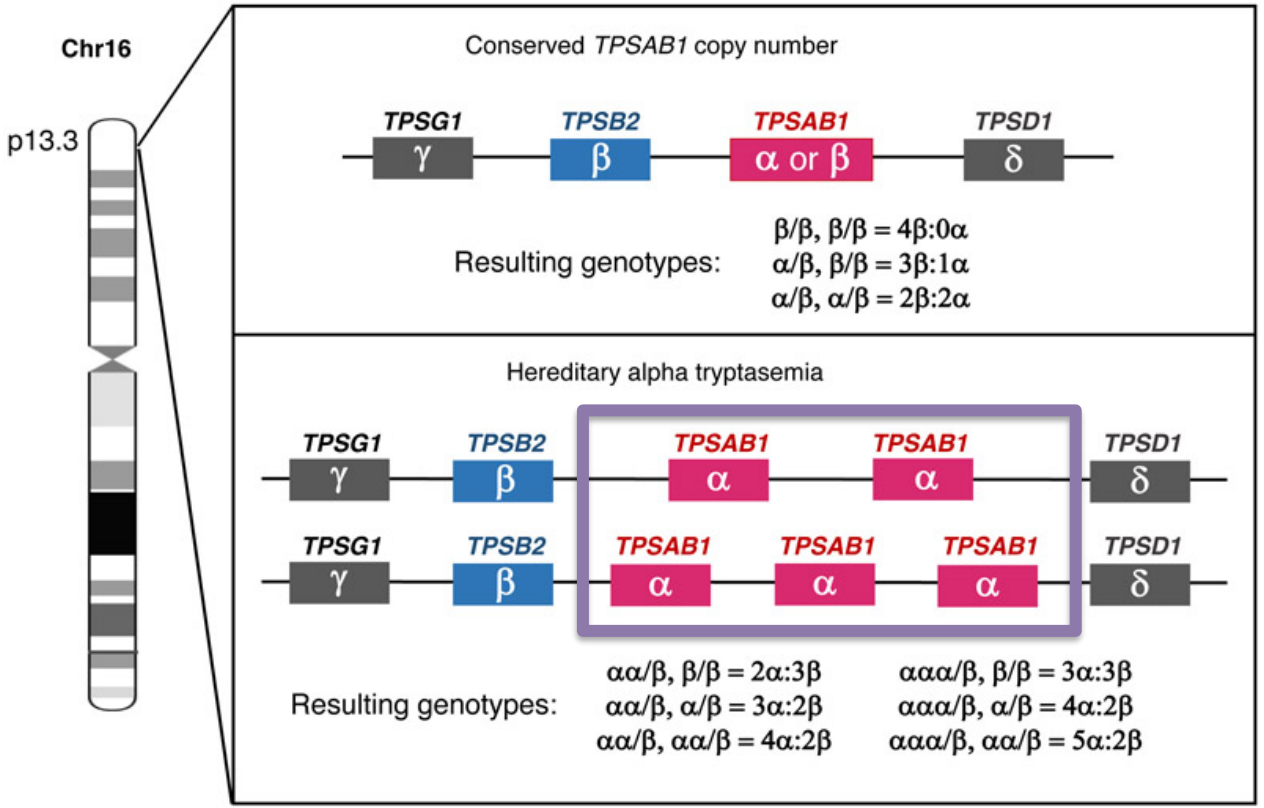
Hereditary Alpha-Tryptasemia

- ~4-6% of the general population has elevated baseline tryptase levels
  - Significant proportion of these patients have been shown to have increased *TPSAB1* copy numbers (duplications and triplications)

- Hereditary alpha-tryptasemia → genetic trait associated with elevated basal tryptase levels (≥ 8 ng/mL) in patients with increased copy numbers in *TPSAB1*

Lyons et al. Immunol Allergy Clin North Am. 2018.
Lyons JJ … Milner JD. Nature Genetics. 2016.
Robey et al. J Allergy Clin Immunol Pract. 2020.

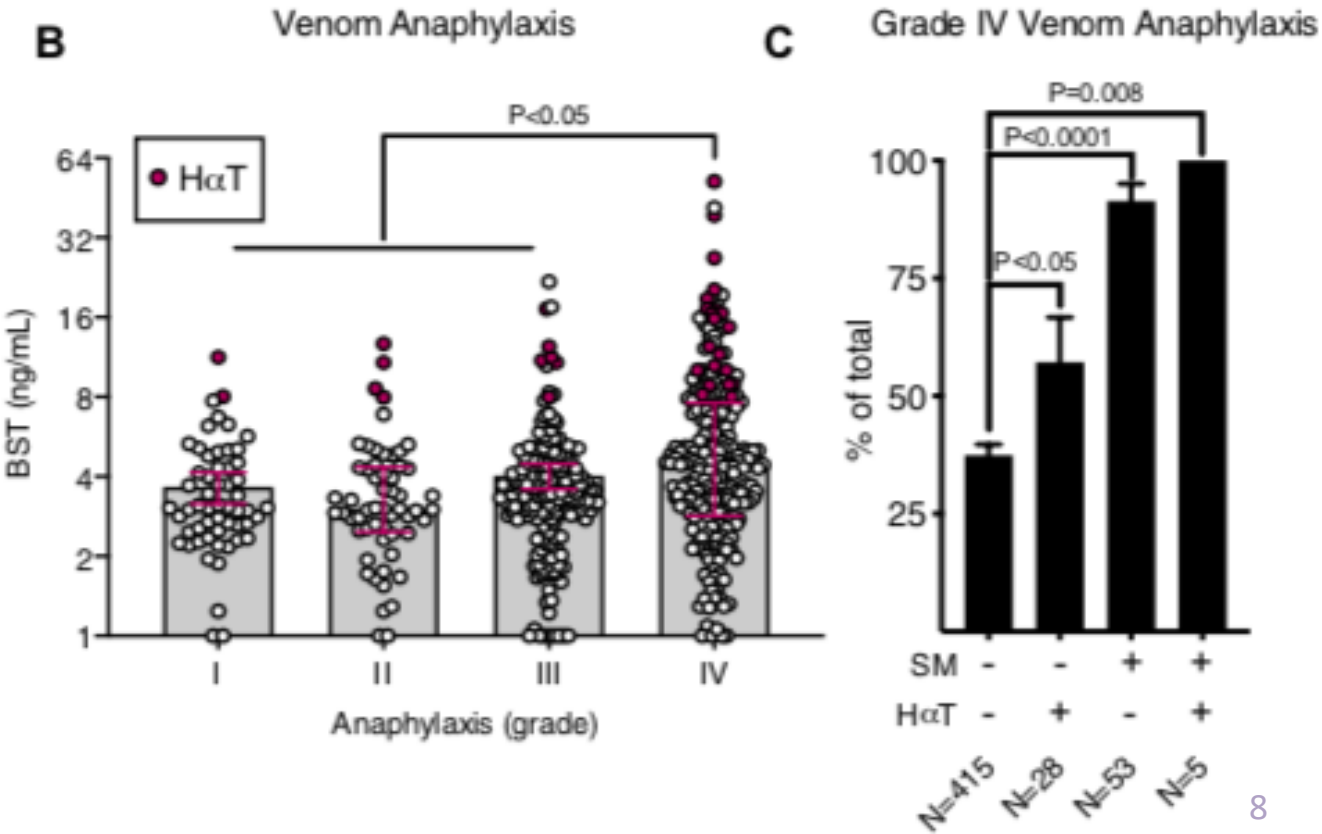
Background



Lyons et al. Immunol Allergy Clin North Am. 2018.
Lyons JJ … Milner JD. Nature Genetics. 2016.

Background

TPSAB1 & Anaphylaxis



Lyons JJ et al. Heritable risk for severe anaphylaxis associated with increased α-tryptase–encoding germline copy number at TPSAB1. J Allergy Clin Immunol, 2021. 147(2): 622-632

Research Question

Do patients with increased *TPSAB1* copy numbers have more severe food allergy reactions?

We hypothesize that children with food allergy and increased *TPSAB1* copy number are more likely to have severe reactions.

Methods

Recruitment

Pilot Study - Inclusion Criteria

1. Children ages 0 to 17 years of age

2. Clinical diagnosis of peanut allergy and reaction to oral food challenge performed by the Division of Allergy and Immunology at Ann and Robert H. Lurie Children's Hospital of Chicago

Methods

Sample Collection & Gene Sequencing

- Non-invasive buccal swabs to collect DNA

- Sequencing of *TPSAB1* to determine copy number by digital droplet PCR
  - Collaboration with Dr. Jonathan Lyons at NIH

Methods

Classification of Severity of Reaction

- Predictor of interest = increased *TPSAB1* copy number

- Outcome variable = severe reaction to food allergen as defined by symptoms during reaction, need for epinephrine, and/or clinician documentation.
  - Also calculated numeric score based on symptoms (modified Bock/PRACTALL)

Sampson HA et al. Second symposium on the definition and management of anaphylaxis: Summary report 2014; Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol, 2006. 117(2):391-397.

Cardona V, Ansotegui IJ, Ebisawa M, et al. World allergy organization anaphylaxis guidance 2020. World Allergy Organ J. 2020;13(10):100472.

Preliminary Results

- Total of 36 peanut-allergic subjects enrolled
  - Results of *TPSAB1* genotyping for 28
- Approximate case/control matching by age and sex
- Majority of subjects male and white

	Control (*n* =10)	Case (*n*= 18)	*p*- value
Female [*n* , (%)]	5 (50.0)	7 (38.9)	0.864
Age at Peanut OFC in Years [median (IQR)]	2 (1.25, 4.5)	3 (2, 6)]	0.36
Self-Identified Race/Ethnicity [*n* , (%)]			0.371
White	7 (70.0)	15 (83.3)	
Hispanic or Latin-X	1 (10.0)	0 (0.0)	
Multiple Races/Ethnicities	2 (20.0)	3 (16.7)	
Eczema History [n, (%)]			0.785
Yes - they have it now	4 (40.0)	8 (44.4)	
Yes, they had it in the past but not now	4 (40.0)	5 (27.8)	
No	2 (20.0)	5 (27.8)	

Preliminary Results

	Control (*n* =10)	Case (*n*= 18)
Total Bock OFC Score median, (IQR)	2 (2, 2)	6.00 (5, 7)
Upper Respiratory/Laryngeal *n* (%)		
Absent	10 (100.0)	10 (55.6)
Mild	0 (0.0)	7 (38.9)
Moderate	0 (0.0)	1 (5.6)
Severe	0 (0.0)	0 (0.0)
Lower Respiratory/Wheezing *n* (%)		
Absent	10 (100.0)	17 (94.4)
Mild	0 (0.0)	1 (5.6)
Moderate	0 (0.0)	0 (0.0)
Severe	0 (0.0)	0 (0.0)
Cardiovascular Symptoms *n* (%)		
Absent	10 (100.0)	14 (77.8)
Mild	0 (0.0)	4 (22.2)
Moderate	0 (0.0)	0 (0.0)
Severe	0 (0.0)	0 (0.0)

Preliminary Results

	Control (*n* =10)	Case (*n*= 18)
Urticaria/Angioedema *n* (%)		
Absent	1 (10.0)	7 (38.9)
Mild	8 (80.0)	6 (33.3)
Moderate	1 (10.0)	3 (16.7)
Severe	0 (0.0)	2 (11.1)
Rash/Erythema *n* (%)		
Absent	3 (30.0)	7 (38.9)
Mild	7 (70.0)	8 (44.4)
Moderate	0 (0.0)	3 (16.7)
Severe	0 (0.0)	0 (0.0)

Preliminary Results

	Control (*n* =10)	Case (*n*= 18)
Reaction Treated with Antihistamine *n* (%)	9 (90.0)	16 (88.9)
Reaction Treated with IM Epinephrine *n* (%)	0 (0.0)	17 (94.4)
Reaction Treated with Steroids *n* (%)	1 (10.0)	6 (33.3)
Reaction Treated with Albuterol *n* (%)	0 (0.0)	0 (0.0)

Preliminary Results

	Control (*n* =10)	Case (*n*= 18)	*p*- value
Whole Peanut sIgE (kU_A/L) mean (SD)	0.59 (0.45)	2.59 (3.34)	0.089
Peanut SPT Wheal size (mm) mean (SD)	5.50 (2.64)	8.00 (3.25)	**0.048**
Ara h 1 sIgE (kU_A/L) mean (SD)	0.01 (0.03)	0.40 (0.63)	0.085
Ara h 2 sIgE (kU_A/L) mean (SD)	0.43 (0.54)	1.15 (1.20)	0.118
Ara h 3 sIgE (kU_A/L) mean (SD)	0.00 (0.00)	0.11 (0.31)	0.31
Ara h 6 sIgE (kU_A/L) mean (SD)	0.60 (0.80)	0.70 (0.42)	0.882
Ara h 8 sIgE (kU_A/L) mean (SD)	0.00 (0.00)	4.82 (9.10)	0.131
Ara h 9 sIgE (kU_A/L) mean (SD)	0.00 (0.00)	0.31 (0.95)	0.341

Preliminary Results

- Genotyped *TPSAB1* in 28 patients to date
- 2/18 (11%) cases with increased alpha tryptase copy number
- Not statistically significant (p=0.524), but 0/10 (0%) controls had increased alpha tryptase copy number

Haploid Tryptase Isoforms

Case 1: aa,b/a,b

Case 2: aa,b/a,b

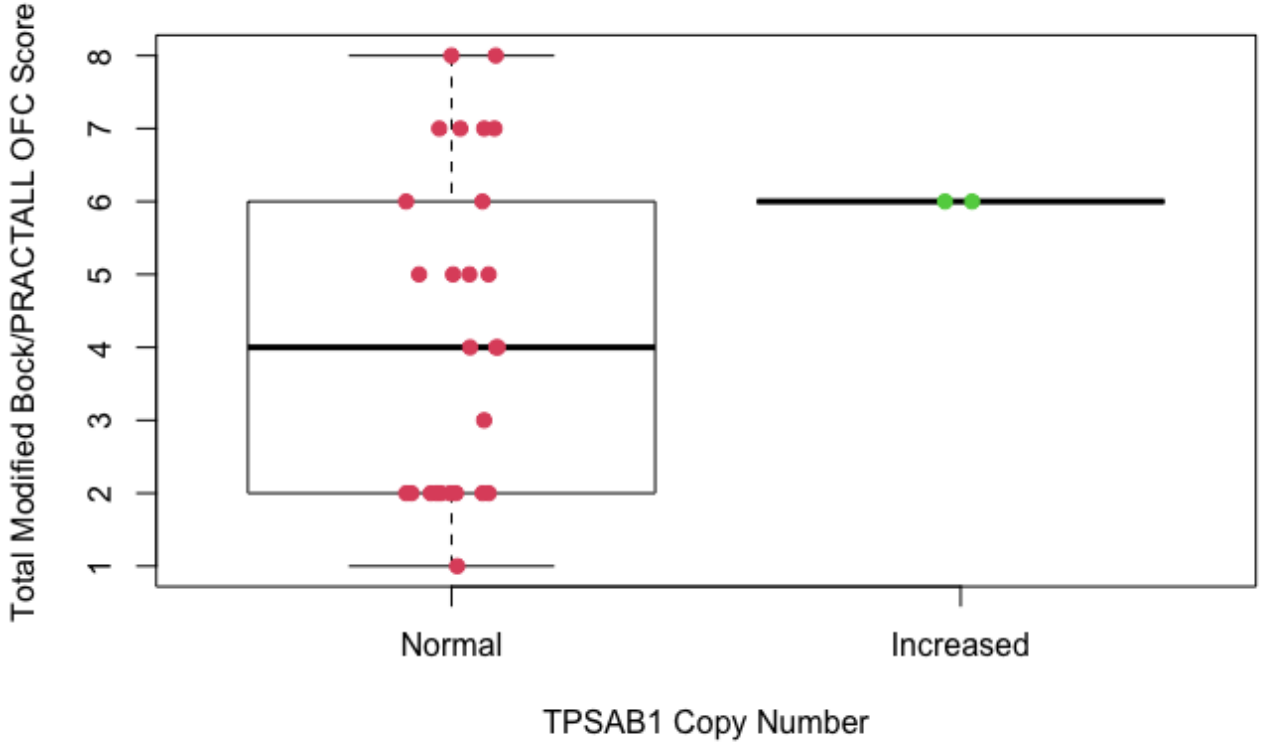
**Both with 3 copies of alpha tryptase ($3\alpha:2\beta$)*

Poll Question

What is the estimated prevalence of increased *TPSAB1* copy number in the general population?

a. 10-12%
b. 0-2%
c. 2-3%
d. 4-6%

Preliminary Results



Conclusions

- Our results provide preliminary data that increased *TPSAB1* copy number may be enriched in patients with severe food allergy reactions

- Rate of increased *TPSAB1* copy number in cases ~2x general population estimates (11% versus 5.5%)
  - Similar to previous findings in cohort of adult patients with *Hymenoptera* venom allergy

Next Steps/Future Directions

- Expansion of pilot project to explore magnitude of association between severity of reactions and *TPSAB1* copy number
- Include other food triggers and subjects presenting to emergency room for treatment of anaphylaxis to capture more severe cases
- Other options include transcriptomic approaches for subjects when acutely reacting to determine differences by genotypes

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Questions?