

ST2⁺CD127⁺ population generally expressed the lowest number of ILC2-related transcripts (Fig 2, A and B). The CD127⁺ populations had the greatest ILC3 signature compared with the CD127⁺ counterparts, whereas the ST2⁺CD127⁺ population had the greatest ILC1 signature. Furthermore, principal-component analysis showed that ST2⁺CD127⁺ and ST2⁺CD127⁺ populations are more similar, compared with the ST2⁺CD127⁺ and ST2⁺CD127⁺ populations, which are individually more unique (Fig 2, C and D). Ccr3, Alox5, and Itgb3 transcripts were increased in the double-positive population and ST2⁺CD127⁺ ILCs showed increased expression of Lta, Tnf, and Hmgb2 (Fig 2, E). ST2⁺CD127⁺ ILCs showed elevated levels of anti-inflammatory cytokines Il10 and Il24, and the ST2⁺CD127⁺ ILCs had ILC1/NK transcript increases in Eomes, Gzma, and Prf1. These results suggest that all populations contain ILC2s as well as unique transcripts supporting overall heterogeneity in the 4 subsets.

Finally, we correlated various transcript markers to the type 2 cytokine transcripts Il5 and Il13 across all populations. Tnfrsf18, which encodes glucocorticoid-induced TNFR family related gene (GITR), showed the strongest correlation with IL-5 and IL-13 transcripts, well above that of Il1rl1 (ST2) and Il7r (CD127) transcripts (Fig 2, F). Mirroring the transcript results, we found that GITR expression more accurately identified IL-5⁺ ILCs from Red5 mice by FACS compared with ST2 in both PBS- and *A alternata*-challenged mice (Fig 2, G). Thus, our work strongly suggests that current methods of ILC2 identification do not sufficiently include the entire type 2 cytokine-producing ILC2 population. Furthermore, our studies highlight the heterogeneity and complexity of ILC responses to *A alternata*, a natural allergen associated with severe asthma.

T.A.D. is supported by NIH grants AI 114585 and AI 070535, D.H.B. is supported by NIH grants AI 070535, AI 107779, and AI 242236, and M.C. is supported by NIH grant AI 070535. We thank Cody Fine and Jesus Olvera of the UCSD Human Embryonic Stem Cell Core for help with cell sorting, the LJI RNA Sequencing Core for help with RNA sequencing (National Institutes of Health Sequencer grant no. S10OD016262), the Histology Core at the University of California, San Diego Moores Cancer Center for help with lung sectioning and staining (National Institutes of Health grant no. P30CA23100), and Karina N. Roman for help with mouse work.

Kellen J. Cavagnero, BS^a

Jana H. Badrani, MS^a

Luay H. Naji, MS^a

Michael B. Amadeo, MS^a

Veranca S. Shah, BS^a

Suzanna Gasparian, BS^a

Alexa Pham, PhD^a

Alice W. Wang, MSc^b

Grégory Seumois, PhD^b

Michael Croft, PhD^{a,b}

David H. Broide, MD^a

Taylor A. Doherty, MD^a

From ^athe Department of Medicine, University of California, San Diego, and ^bthe La Jolla Institute for Allergy and Immunology, La Jolla, Calif. E-mail: tdoherty@ucsd.edu.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

REFERENCES

1. Doherty TA, Broide DH. Airway innate lymphoid cells in the induction and regulation of allergy. *Allergol Int* 2019;68:9-16.
2. Tait Wojno ED, Artis D. Emerging concepts and future challenges in innate lymphoid cell biology. *J Exp Med* 2016;213:2229-48.

3. Bush RK, Prochnau JJ. Alternaria-induced asthma. *J Allergy Clin Immunol* 2004;113:227-34.
4. Doherty TA, Khorram N, Sugimoto K, Sheppard D, Rosenthal P, Cho JY, et al. Alternaria induces STAT6-dependent acute airway eosinophilia and epithelial FIZZ1 expression that promotes airway fibrosis and epithelial thickness. *J Immunol* 2012;188:2622-9.
5. Doherty TA, Khorram N, Chang JE, Kim HK, Rosenthal P, Croft M, et al. STAT6 regulates natural helper cell proliferation during lung inflammation initiated by Alternaria. *Am J Physiol Lung Cell Mol Physiol* 2012;303:L577-88.
6. Bartemes KR, Iijima K, Kobayashi T, Kephart GM, McKenzie AN, Kita H. IL-33-responsive lineage—CD25⁺ CD44(hi) lymphoid cells mediate innate type 2 immunity and allergic inflammation in the lungs. *J Immunol* 2012;188:1503-13.
7. Jurak LM, Xi Y, Landgraf M, Carroll ML, Murray L, Upham JW. Interleukin 33 selectively augments rhinovirus-induced type 2 immune responses in asthmatic but not healthy people. *Front Immunol* 2018;9:1895.
8. Ohne Y, Silver JS, Thompson-Snipes L, Collet MA, Blanck JP, Cantarel BL, et al. IL-1 is a critical regulator of group 2 innate lymphoid cell function and plasticity. *Nat Immunol* 2016;17:646-55.
9. Silver JS, Kearley J, Copenhaver AM, Sanden C, Mori M, Yu L, et al. Inflammatory triggers associated with exacerbations of COPD orchestrate plasticity of group 2 innate lymphoid cells in the lungs. *Nat Immunol* 2016;17:626-33.

Available online July 29, 2019.
<https://doi.org/10.1016/j.jaci.2019.07.018>

Prevalence and characteristics of adult shellfish allergy in the United States



To the Editor:

Shellfish allergy (SA) is one of the most common food allergies worldwide^{1,2} and the third most common in US children.³ Although the isolation of specific shellfish allergens and immunologic mechanisms has improved the understanding of SA pathophysiology,⁴ knowledge gaps remain regarding the prevalence, distribution, and determinants of SAs among US adults.⁵ Consequently, this study estimates national SA prevalence, characteristics, and severity within a large, nationally representative sample of 40,443 US adults surveyed between October 2015 and September 2016. Details regarding survey development, complex survey sampling, weighting, statistical methodologies, and outcomes measures for food allergy assessment—including their unique strengths and limitations—are detailed in Gupta et al.⁶

In short, reported allergies were considered convincingly IgE-mediated if reported symptoms included at least 1 stringent symptom (see Fig E1 in this article's Online Repository at www.jacionline.org) upon ingestion of the responsible allergen. Classification of physician-confirmed and severe allergies is summarized in Fig E2 in this article's Online Repository at www.jacionline.org. For analyses comparing characteristics of crustacean-allergic versus mollusk-allergic adults, individuals reporting both allergies were excluded. Coastal residence was determined at the county level via residential ZIP using National Oceanic and Atmospheric Administration definitions of coastal state, coastal county, and shoreline counties⁷ not bordering the Great Lakes. Please note that because ZIP codes were queried only for participants' current residence, this may lead to inaccurate estimates for respondents who had moved since developing SA.

Population-weighted demographic and atopic disease characteristics are presented in Table I. Mean age of SA diagnosis was 17.7 years (95% CI, 16.6%-18.7%), and mean age of adult-onset SA was 28.3 years (95% CI, 26.9%-29.8%). SA prevalence by allergen types and age categories is presented in Table E1 in this article's Online Repository at www.jacionline.org. Overall,

TABLE I. Demographic characteristics of the study population, % (95% CI)

Variable	All adults	Adults with convincing SA	P value	Adults with convincing crustacean allergy only (no mollusk allergy)	Adults with convincing mollusk allergy only (no crustacean allergy)	P value
Age (y)						
18-29	21.5 (20.8-22.1)	20.5 (17.9-23.4)	.51	18.2 (15.0-22.0)	21.1 (13.5-31.5)	.55
30-39	17.0 (16.5-17.5)	21.0 (18.3-23.9)	.002	20.1 (16.3-24.6)	21.6 (14.5-31.1)	.74
40-49	16.8 (16.3-17.3)	14.6 (12.5-16.9)	.06	14.6 (11.6-18.2)	12.5 (8.0-18.9)	.52
50-59	18.0 (17.5-18.5)	20.2 (17.7-23.0)	.09	20.9 (17.1-25.3)	19.7 (13.9-27.2)	.77
60+	26.8 (26.2-27.4)	23.8 (20.9-26.9)	.05	26.1 (21.7-31.0)	25.1 (18.3-33.5)	.83
Sex						
Female	51.7 (51.0-52.4)	65.0 (61.8-68.1)	<.001	63.6 (58.7-68.3)	62.9 (53.4-71.4)	.89
Male	48.3 (47.6-49.0)	35.0 (31.9-38.2)		36.4 (31.8-41.3)	37.1 (28.6-46.6)	
Race/ethnicity						
Asian, non-Hispanic	3.9 (3.6-4.1)	5.0 (3.9-6.4)	.04	5.9 (4.3-8.1)	5.2 (2.4-11.2)	.77
Black, non-Hispanic	11.7 (11.3-12.1)	13.2 (11.2-15.5)	.15	15.7 (12.5-19.7)	8.6 (4.8-15.0)	.045
White, non-Hispanic	64.9 (64.2-65.6)	57.8 (54.4-61.2)	<.001	56.3 (51.2-61.2)	59.7 (49.8-69.0)	.54
Hispanic/Latino	15.5 (14.9-16.1)	17.9 (15.3-20.9)	.07	15.9 (12.6-19.9)	16.5 (9.4-27.2)	.91
Multiple/other	4.1 (3.8-4.4)	6.1 (4.4-8.4)	.02	6.1 (3.6-10.3)	9.9 (5.3-17.9)	.24
Household income						
<25K	16.6 (16.2-17.1)	17.0 (14.6-19.7)	.77	16.5 (13.5-19.9)	19.7 (12.1-30.4)	.49
25K-49K	22.0 (21.4-22.5)	20.9 (18.5-23.4)	.39	19.8 (16.4-23.8)	18.2 (13.1-24.7)	.64
50K-99K	30.9 (30.3-31.5)	33.8 (30.8-37.0)	.06	33.8 (29.3-38.6)	32.4 (24.6-41.3)	.77
100K-149K	19.6 (19.0-20.2)	20.3 (17.4-23.5)	.67	21.2 (16.8-26.4)	23.4 (16.0-32.9)	.65
150K+	10.9 (10.4-11.5)	8.1 (6.3-10.3)	.01	8.7 (6.1-12.4)	6.3 (3.4-11.6)	.37
Proximity of geographic location to the coast						
Coastal states	60.6 (60.0-61.3)	63.5 (60.3-66.6)	.08	65.0 (60.3-69.4)	63.2 (53.9-71.6)	.73
Inland states	39.4 (38.7-40.0)	36.5 (33.4-39.7)		35.0 (30.6-39.7)	36.8 (28.4-46.1)	
Coastal watershed counties	54.2 (53.5-54.8)	56.5 (53.1-59.8)	.17	57.3 (52.3-62.1)	50.6 (41.2-59.9)	.22
Noncoastal watershed counties	45.9 (45.2-46.5)	43.5 (40.2-46.9)		42.7 (37.9-47.7)	49.4 (40.1-58.8)	
Shoreline counties	41.3 (40.7-42.0)	45.4 (42.1-48.8)	.02	47.7 (42.7-52.7)	39.3 (30.7-48.6)	.12
Nonshoreline counties	58.7 (58.0-59.3)	54.6 (51.2-57.9)		52.3 (47.3-57.3)	60.7 (51.4-69.3)	
Age of SA diagnosis, mean (95% CI)	NA	17.7 (16.6-18.7)	NA	18.8 (17.3-20.3)	21.1 (17.6-24.7)	NA
Age of adult-onset SA diagnosis, mean (95% CI)	NA	28.3 (26.9-29.8)	NA	27.8 (25.6-30.1)	33.9 (29.6-38.2)	NA
Physician-diagnosed comorbidities						
Asthma	12.3 (11.9-12.7)	23.2 (20.6-26.0)	<.001	24.7 (20.7-29.2)	14.4 (9.6-21.0)	.01
Eczema	6.7 (6.4-7.1)	11.8 (9.7-14.2)	<.001	10.1 (7.4-13.8)	12.2 (7.3-19.7)	.54
Allergic rhinitis	21.4 (20.9-22.0)	33.4 (30.3-36.7)	<.001	32.8 (28.2-37.9)	33.9 (25.9-42.8)	.84
Insect sting allergy	3.8 (3.6-4.1)	7.6 (6.2-9.4)	<.001	7.0 (4.9-9.7)	7.5 (4.2-12.9)	.84
Latex allergy	2.3 (2.1-2.5)	5.4 (4.2-6.9)	<.001	4.8 (3.0-7.5)	3.2 (1.5-6.8)	.37
Medication allergy	13.4 (13.0-13.9)	24.1 (21.2-27.1)	<.001	25.9 (21.5-30.9)	23.7 (17.2-31.9)	.63
Urticaria/chronic hives	0.9 (0.8-1.0)	2.5 (1.7-3.5)	<.001	2.6 (1.5-4.3)	2.1 (0.8-5.5)	.73
Family history of allergic diseases						
Parental asthma	13.5 (13.1-14.0)	22.2 (19.4-25.3)	<.001	25.5 (21.0-30.5)	14.4 (8.9-22.4)	.02
Parental eczema	9.6 (9.2-10.0)	15.9 (13.4-18.7)	<.001	14.2 (11.0-18.1)	17.3 (10.6-27.0)	.47
Parental environmental allergies	28.7 (28.0-29.4)	38.6 (35.1-42.2)	<.001	38.8 (33.6-44.2)	40.4 (30.6-51.0)	.78
Parental FA	12.9 (12.4-13.4)	37.1 (33.5-40.9)	<.001	34.3 (29.2-39.9)	43.3 (32.8-54.6)	.14
Sibling(s) with FA	16.6 (16.1-17.2)	33.8 (30.4-37.4)	<.001	37.4 (32.0-43.0)	26.9 (19.1-36.3)	.05

FA, Food allergy; NA, not applicable/available.

the estimated SA prevalence was 2.9% (2.7%-3.1%), whereas physician-confirmed SA prevalence was 1.2% (1.1%-1.3%). Among all adults, 2.4% were estimated to be crustacean-allergic, whereas 1.2% were estimated to have a physician-confirmed crustacean allergy. In addition, 1.6% were estimated to be mollusk-allergic, with 0.5% estimated as having a physician-confirmed mollusk allergy.

Table E2 in this article's Online Repository at www.jacionline.org presents the distribution of symptom characteristics, allergy severity, and outcomes among adults with SA. Skin/mucosal and respiratory symptoms (eg, nasal congestion and wheezing) were more commonly reported by crustacean- than by mollusk-

allergic adults. In contrast, gastrointestinal symptoms were more common among mollusk-allergic patients. In addition, crustacean-allergic adults may be more likely to develop SA during adulthood (54.4%) compared with mollusk-allergic adults (45.8%) ($P = .11$).

Table II reports adjusted associations among key demographic/comorbid atopic disease characteristics and SA outcomes. Adults reporting nonwhite races/ethnicity were more likely to have SA and crustacean allergy compared with their white (non-Hispanic) counterparts. In addition, adults living in ocean-adjacent (shoreline) counties had elevated odds of having SA compared with those living in nonshoreline counties (odds ratio [OR], 1.2; 95%

TABLE II. Adjusted associations for demographic characteristics, comorbid diseases, and severity of the diagnosis among adults with SA and SA subgroups

Variable	Odds of convincing SA among all adults (95% CI)	Odds of convincing crustacean allergy only among all adults (95% CI)	Odds of convincing mollusk allergy only among all adults (95% CI)	Odds of severe shellfish reactions among adults with convincing SA (95% CI)	Odds of severe shellfish reactions among adults with convincing crustacean allergy only (95% CI)	Odds of severe shellfish reactions among adults with convincing mollusk allergy only (95% CI)	Adult-onset SA among adults with convincing SA (95% CI)
Shoreline county							
Yes vs no	1.2 (1.1-1.4)	1.3 (1.1-1.6)	0.9 (0.6-1.4)	0.8 (0.6-1.0)	0.6 (0.4-0.9)	0.8 (0.4-1.8)	1.3 (1.0-1.8)
Race/ethnicity (vs white, non-Hispanic)							
Asian, non-Hispanic	1.7 (1.3-2.2)	2.1 (1.5-3.0)	1.7 (0.7-4.2)	0.9 (0.5-1.7)	1.1 (0.5-2.3)	2.1 (0.5-9.5)	1.0 (0.6-1.8)
Black, non-Hispanic	1.3 (1.1-1.6)	1.7 (1.3-2.2)	0.8 (0.4-1.7)	1.9 (1.2-2.8)	2.2 (1.2-3.9)	2.1 (0.6-7.1)	1.0 (0.7-1.6)
Hispanic	1.4 (1.1-1.7)	1.3 (1.0-1.7)	1.3 (0.7-2.4)	1.2 (0.8-1.7)	1.0 (0.6-1.7)	1.2 (0.4-3.8)	1.0 (0.7-1.5)
Multiple/other	1.6 (1.1-2.3)	1.7 (0.9-3.0)	2.6 (1.3-5.2)	0.6 (0.3-1.2)	0.6 (0.2-2.0)	1.6 (0.3-8.3)	0.9 (0.5-1.6)
Sex							
Female vs male	1.5 (1.3-1.7)	1.4 (1.1-1.8)	1.4 (0.9-2.1)	1.0 (0.7-1.3)	1.0 (0.7-1.5)	0.6 (0.3-1.3)	1.6 (1.2-2.2)
Age (vs < 30 y)							
30-39	1.3 (1.1-1.6)	1.4 (1.0-1.9)	1.3 (0.7-2.4)	0.8 (0.5-1.2)	0.9 (0.5-1.7)	0.4 (0.1-1.4)	3.0 (1.9-4.9)
40-49	0.9 (0.7-1.1)	1.0 (0.7-1.4)	0.8 (0.4-1.4)	1.1 (0.7-1.7)	0.9 (0.5-1.8)	1.2 (0.3-4.3)	4.5 (2.7-7.4)
50-59	1.2 (0.9-1.5)	1.3 (1.0-1.8)	1.1 (0.6-1.9)	0.9 (0.6-1.3)	1.0 (0.5-1.8)	0.5 (0.1-1.6)	5.2 (3.2-8.4)
60+	0.9 (0.8-1.2)	1.1 (0.8-1.5)	0.9 (0.5-1.6)	0.5 (0.3-0.7)	0.5 (0.3-1.0)	0.3 (0.1-0.9)	14.4 (8.8-23.6)
Household income (\$)							
25,000-49,999	1.0 (.8-1.2)	1.0 (0.7-1.3)	0.7 (0.4-1.3)	0.8 (0.5-1.2)	1.1 (0.6-2.0)	0.3 (0.1-0.9)	1.0 (0.7-1.6)
50,000-99,999	1.2 (1.0-1.4)	1.2 (.9-1.6)	0.9 (0.5-1.6)	0.8 (0.5-1.2)	1.3 (0.7-2.2)	0.3 (0.1-1.1)	1.0 (0.7-1.5)
100,000-149,000	1.1 (.9-1.4)	1.2 (.9-1.7)	1.0 (0.5-2.0)	0.8 (0.5-1.3)	1.5 (0.8-3.0)	0.6 (0.1-2.5)	1.2 (0.7-2.0)
>150,000	0.8 (0.6-1.1)	0.9 (0.6-1.4)	0.5 (0.2-1.1)	0.8 (0.5-1.6)	1.7 (0.7-4.1)	0.9 (0.2-4.4)	0.9 (0.5-1.7)
Comorbid conditions (vs not)							
Asthma	1.7 (1.4-2.0)	1.9 (1.5-2.4)	0.9 (0.5-1.4)	1.1 (0.8-1.5)	1.1 (0.7-1.7)	1.1 (0.4-2.7)	1.0 (0.7-1.4)
Atopic dermatitis	1.4 (1.1-1.7)	1.1 (0.8-1.6)	1.6 (0.5-1.4)	1.6 (1.2-2.2)	1.0 (0.5-2.0)	0.5 (0.1-1.6)	1.1 (0.7-1.8)
Allergic rhinitis	1.4 (1.2-1.7)	1.3 (1.0-1.7)	1.6 (1.1-2.4)	1.6 (1.2-2.2)	1.4 (0.9-2.3)	2.5 (1.0-6.3)	1.5 (1.0-2.0)
Insect sting allergy	1.4 (1.1-1.8)	1.2 (0.8-1.8)	1.4 (0.8-2.6)	2.6 (1.5-4.5)	2.7 (1.1-6.6)	1.8 (0.5-6.9)	0.8 (0.5-1.3)
Latex allergy	1.5 (1.1-2.0)	1.3 (0.8-2.1)	0.8 (0.4-1.8)	1.3 (0.6-2.5)	1.5 (0.4-5.9)	1.0 (0.3-3.8)	0.8 (0.4-1.4)
Medication allergy	1.6 (1.4-2.0)	1.9 (1.4-2.5)	1.6 (1.1-2.4)	0.9 (0.6-1.3)	0.7 (0.4-1.3)	1.4 (0.6-3.5)	1.2 (0.8-1.9)
Urticaria/hives	1.6 (1.1-2.4)	1.6 (0.9-2.9)	1.4 (0.5-3.8)	0.8 (0.4-1.6)	0.8 (0.3-2.3)	0.7 (0.1-6.5)	0.7 (0.3-1.7)

CI, 1.1-1.4). Shoreline county residence was also significantly associated with having only crustacean allergy (ie, no mollusk allergy) (OR, 1.3; 95% CI, 1.1-1.6); however, a similar trend was not observed with having only mollusk allergy.

Risk of severe shellfish reaction also differed by demographic characteristics, such that black (non-Hispanic) race was associated with increased odds of severe reactions among adults with SA (OR, 1.9; 95% CI, 1.2-2.8) and crustacean allergy (OR, 2.2; 95% CI, 1.2-3.9), but not mollusk allergy (OR, 0.8; 95% CI, 0.4-1.7). Adults older than 60 years had decreased odds of having severe allergic reactions to shellfish (OR, 0.5; 95% CI, 0.3-0.7), with a similar pattern reported for those with mollusk allergy (OR, 0.3; 95% CI, 0.1-0.9). Interestingly, shoreline county residence appears to be linked to reduced odds of severe shellfish reactions (OR, 0.8; 95% CI, 0.6-1.0) compared with those living in nonshoreline counties, with significant protective effects observed among adults with only crustacean allergy (OR, 0.6; 95% CI, 0.4-0.9). Data also indicate that current residence in a shoreline county may increase odds of adult-onset SA (OR, 1.3; 95% CI, 1.0-1.8). In addition, having a comorbid insect sting/venom allergy was associated with greater odds of having a severe crustacean allergy (OR, 2.7; 95% CI, 1.1-6.6), whereas comorbid

allergic rhinitis was associated with greater odds of a severe mollusk allergy (OR, 2.5; 95% CI, 1.0-6.3) as well as greater odds of adult-onset SA (OR, 1.5; 95% CI, 1.0-2.0).

Rates of comorbidities among shellfish and other food allergies are presented in Table E3 in this article's Online Repository at www.jacionline.org. The highest rates were observed among crustacean allergens and between crustacean and mollusk allergy. Fin fish allergy (18.4%) was the second most common allergy among adults with SA. Among adults with mollusk allergy, the most common accompanying allergy was shrimp (56.2%), followed by lobster (53.6%) and crab (53.1%), with an overall 70.2% cross-reactivity with crustacea.

Overall, SA is estimated to affect nearly 3% of US adults, half of whom report developing SA during adulthood. This updates national data collected in 2002, which reported adult SA prevalence rates of 2.6%, and also observed elevated rates among female and nonwhite adults.⁸ In our study, adult mollusk allergy prevalence was 1.6%—significantly lower than the estimated crustacean allergy prevalence of 2.4%.

Although nearly half (45%) of shellfish-allergic adults reported visiting the emergency department for food allergy treatment within their lifetime, not all adults with SA experience severe

reactions. These data indicate that more than 40% of shellfish-allergic adults report only mild to moderate reactions. Interestingly, reaction profiles appeared somewhat different among uniquely crustacean- and mollusk-allergic adults, in that a greater proportion of adults with crustacean allergy reported skin/mucosal symptoms and wheezing symptoms with fewer gastrointestinal symptoms compared with mollusk-allergic adults. Crustacean-allergic adults also appear to have slightly higher rates of adult-onset SA compared with mollusk-allergic adults.

Previous studies of coastal Asian populations reported high rates of SA, suggesting a relationship between greater shellfish allergen exposure and SA risk.⁹ Here, odds of current SA and crustacean allergy were significantly elevated among adults living in a shoreline county. However, despite presenting with an increased risk, crustacean-allergic adults residing in shoreline counties had decreased odds of severe reactions.

Despite previous research indicating high cross-reactivity among shellfish allergens,⁴ limited epidemiological work has addressed this issue.⁵ Although Sicherer et al⁸ reported that 14% of respondents with crustacean allergy also reported a mollusk allergy, in our study 46% of crustacean-allergic adults were also mollusk-allergic. Strikingly, 70.2% of mollusk-allergic adults in our study were also crustacean-allergic, suggesting that there may be greater clinical cross-reactivity between crustacean and mollusk allergens than previously acknowledged. Moreover, nearly 1 in 5 adults with SA had comorbid fin fish allergy, with higher rates observed among mollusk-allergic adults. However, further studies incorporating standardized confirmatory allergy testing are clearly warranted to replicate these population-based, self-report survey data.

Given the substantial population-level burden of SA identified here, we hope this study will raise awareness and spur further research to better understand, treat, and prevent crustacean and mollusk allergies among US adults.

We thank the National Institute of Allergy and Infectious Diseases for providing financial support for the study.

Christopher M. Warren, PhD^a

Ozge N. Aktas, MD^b

Ruchi S. Gupta, MD, MPH^{c,d}

Carla M. Davis, MD^e

From ^athe Institute for Public Health and Medicine, Feinberg School of Medicine, Northwestern University, ^bthe Department of Pediatrics, University of Illinois College of Medicine at Chicago, ^cthe Departments of Pediatrics and Medicine, Feinberg School of Medicine, Northwestern University, and ^dMary Ann & J. Milburn Smith Child Health Research, Outreach, and Advocacy Center, Ann & Robert H. Lurie Children's Hospital, Chicago, Ill; and ^ethe Section of Immunology, Allergy, Rheumatology and Retrovirology, Department of Pediatrics, Baylor College of Medicine, Texas Children's Hospital, Houston, Tex. E-mail: r-gupta@northwestern.edu.

This study was funded by the National Institute of Allergy and Infectious Diseases, "US Prevalence, Distribution and Determinants of Adult and Childhood Food Allergy" (grant no. R21AI135702—PI: R.S.G.).

Disclosure of potential conflicts of interest: C. M. Warren reports grant support from the National Institutes of Health (NIH). R. S. Gupta reports receiving grants from the NIH, Stanford University, and Aimmune Therapeutics during the conduct of the study; serving as a medical consultant/advisor for DBV, Aimmune, Before Brands, Pfizer, Mylan, and Kaleo, Inc, over the past 3 years; and receiving grants from the NIH, Allergy and Asthma Network, Food Allergy Research & Education, Rho Inc, Northwestern University Clinical and Translational Sciences Institute, Thermo Fisher, United Health Group, Mylan, and the National Confectioners Association outside the submitted work. C. M. Davis reports research grants and contracts from the following entities: National Institute of Allergy and Infectious Diseases, Aimmune Therapeutics, Inc, DBV Technologies, Inc, Thermo Fisher Scientific, Inc,

Nutricia North America, Regeneron Pharmaceuticals, and Moonlight Therapeutics, Inc. O. N. Aktas declares no relevant conflicts of interest.

REFERENCES

- Steinke M, Fiocchi A, Kirchlechner V, Ballmer-Weber B, Brockow K, Hischenhuber C, et al. Perceived food allergy in children in 10 European nations: a randomised telephone survey. *Int Arch Allergy Immunol* 2007;143:290-5.
- National Academies of Sciences, Engineering, and Medicine. Finding a path to safety in food allergy: assessment of the global burden, causes, prevention, management, and public policy. Washington, DC: The National Academies Press; 2017. Available at: <https://doi.org/10.17226/23658>.
- Gupta RS, Warren CM, Smith BM, Blumenstock JA, Jiang J, Davis M, et al. The public health impact of parent-reported childhood food allergies in the United States. *Pediatrics* 2018;142.
- Leung NY, Wai CY, Shu S, Wang J, Kenny TP, Chu KH, et al. Current immunological and molecular biological perspectives on seafood allergy: a comprehensive review. *Clin Rev Allergy Immunol* 2014;46:180-97.
- Moonesinghe H, Mackenzie H, Venter C, Kilburn S, Turner P, Weir K, et al. Prevalence of fish and shellfish allergy: a systematic review. *Ann Allergy Asthma Immunol* 2016;117:264-72.e264.
- Gupta RS, Warren CM, Smith BM, Jiang J, Blumenstock JA, Davis MM, et al. Prevalence and severity of food allergies among US adults. *JAMA Netw Open* 2019;2:e185630.
- NOAA Office for Coastal Management. Coastal county definitions. 2017. Available at: <https://coast.noaa.gov/data/digitalcoast/pdf/qrt-coastal-county-definitions.pdf>. Accessed May 2, 2019.
- Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of seafood allergy in the United States determined by a random telephone survey. *J Allergy Clin Immunol* 2004;114:159-65.
- Shek LP, Cabrera-Morales EA, Soh SE, Gerez I, Ng PZ, Yi FC, et al. A population-based questionnaire survey on the prevalence of peanut, tree nut, and shellfish allergy in 2 Asian populations. *J Allergy Clin Immunol* 2010;126:324-31, 331.e1-7.

Available online August 8, 2019.

<https://doi.org/10.1016/j.jaci.2019.07.031>

Functional evaluation of the pathological significance of *MEFV* variants using induced pluripotent stem cell-derived macrophages



To the Editor:

Familial Mediterranean fever (FMF) is the most common hereditary autoinflammatory disorder. It is characterized by recurrent episodes of fever, polyserositis, and abdominal pain. FMF is associated with mutations in the *MEFV* gene, which encodes the inflammasome adaptor pyrin. Pyrin is an inflammasome sensor that detects imbalances in Rho GTPase activity, which can be caused by bacterial effectors or bacterial toxins. Clostridial toxins are glycosylating enzymes that inactivate the RhoA GTPase, which results in activation of the pyrin inflammasome, activation of caspase-1, release of the proinflammatory cytokines IL-1 β and IL-18, and an inflammatory cell death termed pyroptosis.

More than 340 *MEFV* variants have been recorded in *Infevers*, an online database of autoinflammatory mutations. Among the *MEFV* variants, M694V and M694I in exon 10 were demonstrated in a systematic review to be related to a severe disease phenotype.¹ Other *MEFV* variants are associated with variable disease severity. The complexity of the clinical phenotype and its association with *MEFV* variants leads to difficulty in assessing the pathogenicity of variants identified in clinical settings.

☐ <u>Skin/Oral Mucosa Symptoms</u> ☐ Hives ☐ Itching ☐ Rash ☐ Swelling (except lip/tongue swelling) ☐ Lip/tongue swelling ☐ Difficulty swallowing ☐ Hoarse voice ☐ Itchy mouth ☐ Throat tightening ☐ Mouth or throat tingling ☐ Other: _____	☐ <u>Gastrointestinal (GI) Symptoms</u> ☐ Belly pain ☐ Cramps ☐ Diarrhea ☐ Nausea ☐ Vomiting ☐ Other: _____
☐ <u>Respiratory Symptoms</u> ☐ Chest tightening ☐ Nasal congestion ☐ Repetitive cough ☐ Trouble breathing ☐ Wheezing ☐ Other: _____	☐ <u>Cardiovascular/Heart Symptoms</u> ☐ Chest pain ☐ Rapid heart rate ☐ Fainting, dizziness, or feeling light headed ☐ Low blood pressure ☐ Other: _____
☐ <u>Other Symptoms</u> ☐ Anxiety ☐ Feeling of impending doom ☐ Headache ☐ Other: _____	

All symptoms listed are offered as answer choices in the survey. Symptoms in bold italics comprised our expert panel's stringent symptom list. A "convincing" food allergy required the report of at least one stringent symptom during the participant's most severe reaction to a given food.

FIG E1. List of allergic reaction symptoms highlighting stringent symptoms indicative of convincing food allergy.

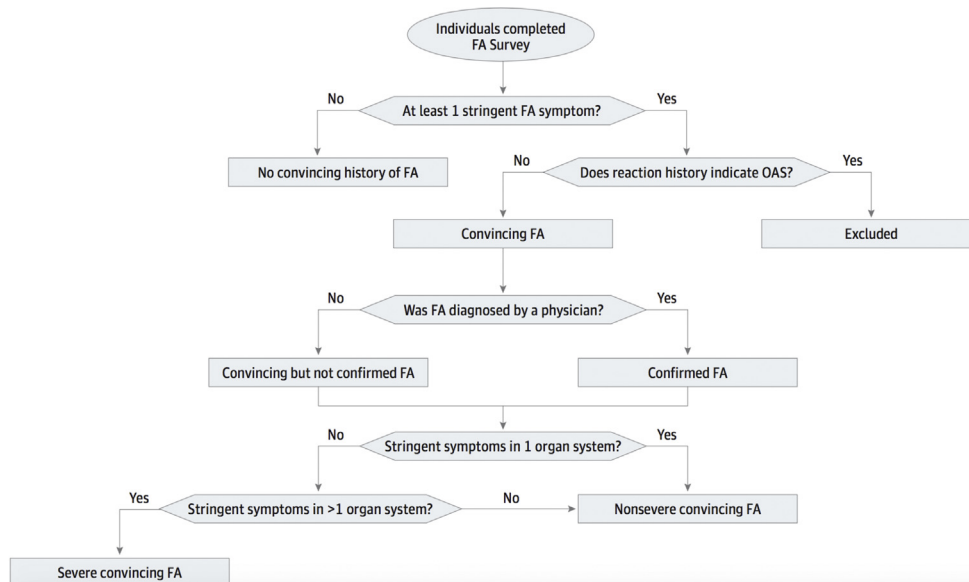


FIG E2. Convincing, physician-confirmed, and severe FA categorization flow diagram. FA, Food allergy; OAS, oral allergy syndrome.

TABLE E1. Prevalence estimates of shellfish, crustacean, and mollusk allergy among adults in the United States, % (95% CI)

Age groups	US adults with convincing SA	US adults with any convincing crustacean allergy	US adults with any convincing mollusk allergy	US adults with convincing crustacean allergy only (no mollusk allergy)	US adults with convincing mollusk allergy only (no crustacean allergy)
Convincing SA prevalence among all adults					
All ages	2.9 (2.7-3.1)	2.4 (2.3-2.6)	1.6 (1.4-1.7)	1.3 (1.2-1.5)	0.5 (0.4-0.6)
18-29 y	2.8 (2.4-3.2)	2.3 (2.0-2.7)	1.6 (1.3-2.0)	1.1 (0.9-1.4)	0.5 (0.3-0.8)
30-39 y	3.6 (3.1-4.2)	3.0 (2.6-3.5)	2.0 (1.7-2.5)	1.6 (1.2-2.0)	0.6 (0.4-0.9)
40-49 y	2.5 (2.2-3.0)	2.2 (1.8-2.6)	1.3 (1.1-1.7)	1.2 (0.9-1.5)	0.4 (0.2-0.5)
50-59 y	3.3 (2.8-3.8)	2.7 (2.4-3.2)	1.7 (1.4-2.0)	1.5 (1.2-1.9)	0.5 (0.4-0.7)
60+ y	2.6 (2.2-3.0)	2.1 (1.8-2.5)	1.2 (1.0-1.5)	1.3 (1.0-1.6)	0.4 (0.3-0.6)
Physician-confirmed SA prevalence among all adults					
All ages	1.2 (1.1-1.3)	1.1 (.95-1.15)	0.5 (0.5-0.6)	0.7 (0.6-0.8)	0.2 (0.1-0.2)
18-29 y	1.3 (1.1-1.5)	1.1 (0.9-1.3)	0.6 (0.4-0.7)	0.7 (0.6-0.9)	0.2 (0.1-0.4)
30-39 y	1.6 (1.4-1.9)	1.4 (1.2-1.7)	0.7 (0.5-0.9)	0.9 (0.7-1.2)	0.2 (0.1-0.3)
40-49 y	1.3 (1.0-1.6)	1.1 (0.9-1.4)	0.5 (0.4-0.8)	0.7 (0.5-1.0)	0.2 (0.1-0.3)
50-59 y	1.5 (1.2-1.8)	1.3 (1.1-1.6)	0.7 (0.5-0.9)	0.8 (0.6-1.1)	0.1 (0.1-0.2)
60+ y	0.7 (0.6-0.9)	.6 (.5-.7)	0.3 (0.2-0.4)	0.4 (0.3-0.6)	0.1 (0.1-0.3)

TABLE E2. Symptom characteristics and outcomes of adults with SA, % (95% CI)

Symptoms and outcomes	All shellfish	Adults with convincing crustacean allergy only	Adults with convincing mollusk allergy only	P value comparing symptoms between crustacean and mollusk-allergic adults
Skin/oral/mucosal tissue				
Any skin/oral/mucosal tissue reaction symptom(s) to shellfish	90.7 (88.5-92.5)	93.1 (90.4-95.1)	77.0 (68.1-84.0)	<.001
Any stringent skin/oral/mucosal tissue symptom(s) to shellfish	74.0 (70.9-76.9)	76.3 (72.0-80.1)	53.1 (43.6-62.3)	<.001
Hives	64.9 (61.6-68.0)	66.7 (62.0-71.1)	48.7 (39.4-58.1)	<.001
Itching	65.3 (62.0-68.5)	65.2 (60.2-69.9)	47.3 (38.0-56.7)	<.001
Rash	49.1 (45.7-52.5)	47.6 (42.6-52.7)	36.9 (28.0-46.9)	.06
Swelling	35.0 (31.8-38.3)	34.0 (29.6-38.8)	22.0 (14.5-32.0)	.03
Lip/tongue swelling	37.7 (34.4-41.0)	37.0 (32.2-42.1)	18.8 (12.9-26.5)	<.001
Difficulty swallowing	39.2 (36.0-42.5)	33.1 (28.6-37.9)	29.6 (21.2-39.8)	.53
Hoarse voice	16.9 (14.6-19.6)	16.6 (13.1-20.8)	8.8 (4.8-15.6)	.04
Itchy mouth	32.8 (29.8-36.1)	29.8 (25.6-34.4)	22.8 (15.0-33.0)	.20
Throat tightening	35.4 (32.3-38.4)	30.8 (26.6-35.4)	27.0 (18.9-37.1)	.48
Mouth or throat tingling	23.8 (21.0-26.9)	22.0 (18.0-26.7)	19.0 (11.4-29.9)	.57
Respiratory				
Any respiratory reaction symptom(s) to shellfish	53.3 (49.9-56.6)	51.3 (46.2-56.3)	43.5 (34.3-53.1)	.16
Any stringent respiratory reaction symptom(s) to shellfish	45.8 (42.5-49.2)	44.2 (39.3-49.2)	34.8 (25.9-44.8)	.10
Chest tightening	22.7 (20.0-25.6)	21.1 (17.5-25.3)	18.1 (10.8-28.9)	.57
Nasal congestion	15.1 (13.0-17.4)	12.2 (9.5-15.4)	7.1 (4.4-11.4)	.046
Repetitive cough	12.9 (10.9-15.3)	9.9 (7.6-12.8)	7.1 (3.7-13.4)	.36
Trouble breathing	31.9 (28.8-35.1)	27.5 (23.2-32.2)	19.5 (13.1-28.0)	.09
Wheezing	18.9 (16.4-21.7)	17.6 (14.0-21.9)	7.6 (4.3-13.0)	.003
Gastrointestinal				
Any gastrointestinal reaction symptom(s) to shellfish	53.8 (50.4-57.1)	45.5 (40.6-50.5)	63.6 (54.3-72.0)	<.001
Any stringent gastrointestinal reaction symptom(s) to shellfish	29.9 (26.9-33.1)	22.0 (18.2-26.3)	40.9 (32.1-50.4)	<.001
Belly pain	24.7 (21.9-27.7)	18.3 (15.0-22.1)	25.9 (18.9-34.5)	.06
Cramps	24.6 (21.9-27.6)	17.9 (14.7-21.8)	30.2 (22.4-39.3)	.004
Diarrhea	22.9 (20.2-25.8)	19.0 (15.6-22.9)	28.7 (20.6-38.5)	.03
Nausea	33.7 (30.5-37.0)	25.9 (21.8-30.5)	43.4 (34.1-53.3)	<.001
Vomiting	29.8 (26.8-33.0)	21.8 (18.0-26.1)	40.8 (32.0-50.2)	<.001
Cardiovascular				
Any cardiovascular reaction symptom(s) to shellfish	33.6 (30.4-36.8)	28.4 (24.3-32.9)	30.2 (21.9-40.0)	.73
Any stringent cardiovascular reaction symptom(s) to shellfish	32.7 (29.6-35.9)	27.0 (23.0-31.4)	29.0 (20.8-38.8)	.69
Chest pain	9.7 (8.0-11.9)	5.9 (4.1-8.4)	6.4 (3.3-12.1)	.83
Rapid heart rate	17.9 (15.5-20.6)	14.2 (11.4-17.6)	10.4 (6.7-15.9)	.21
Fainting, dizziness, or feeling lightheaded	18.0 (15.5-20.9)	15.0 (11.8-18.9)	16.6 (9.5-27.3)	.74
Low blood pressure	4.5 (3.4-5.9)	3.3 (2.2-4.9)	1.9 (0.7-5.0)	.31
SA outcomes				
Only mild to moderate reactions to shellfish	43.2 (39.9-46.6)	46.9 (41.9-51.9)	53.7 (44.2-63.0)	.22
1+ severe reactions to shellfish	56.8 (53.4-60.1)	53.1 (48.1-58.1)	46.3 (37.1-55.9)	
1+ lifetime FA-related ED visit	45.3 (42.0-48.6)	39.1 (34.5-43.9)	38.7 (29.8-48.4)	.94
1+ last year FA-related ED visits	11.1 (9.0-13.5)	9.6 (7.5-12.3)	12.1 (5.9-23.1)	.55
1+ adult-onset shellfish allergy	48.2 (44.8-51.6)	54.4 (49.4-59.3)	45.8 (36.7-55.2)	.11

Symptoms in boldface italics comprised our expert panel's stringent symptom list.

ED, Emergency department; FA, food allergy.

TABLE E3. Reported prevalence of specific convincingly IgE-mediated food allergies among shellfish-allergic US adults

Specific food allergy	% of adults with each row allergy who also are allergic to the column allergen												
	Mollusk	Crustacean	Shrimp	Lobster	Crab	Fin fish	Peanut	Milk	Tree nut	Egg	Wheat	Soy	Sesame
Shellfish	54.3	83.3	65.9	43.7	46.0	18.4	13.1	10.9	9.1	5.3	5.1	4.9	2.2
Mollusk	100	70.2	56.2	53.6	53.1	25.6	14.2	12.2	9.8	5.2	6.1	5.2	2.2
Crustacean	45.8	100	79.1	52.5	55.2	20.4	14.1	11.0	9.7	5.9	4.9	4.7	2.5
Shrimp	46.3	100	100	49.5	51.7	21.1	13.8	11.9	9.1	5.6	5.5	4.9	2.3
Lobster	66.5	100	74.5	100	76.0	27.5	15.3	11.4	11.5	7.1	5.2	5.5	2.8
Crab	62.6	100	74.1	72.3	100	25.2	16.2	10.5	10.6	6.4	5.7	5.3	2.9