

High Frequency of Atopy with geographic variation in non-cystic fibrosis bronchiectasis

Pei Yee Tiew^{1,2}, Michéal Mac Aogáin¹, Albert Yick Hou Lim³, Teck Boon Low⁴, Gan Liang Tan², Tidi Maharani Hassan⁷, Sze Lei Pang⁶, Zi Yang Lee⁶, Xiao Wei Gwee⁶, Christopher Martinus⁶, Yang Yie Sio⁶, Sri Anusha Matta⁶, Thun How Ong^{2,5}, Holly R. Keir⁸, Mariko Siyue Koh^{2,5}, John Abisheganaden³, James D. Chalmers⁸, Fook Tim Chew⁶, Sanjay Haresh Chotirmall¹

¹Lee Kong Chian School of Medicine, Nanyang Technological University Singapore, ²Department of Respiratory and Critical Care Medicine, Singapore General Hospital, Singapore, ³Department of Respiratory and Critical Care Medicine, Tan Tock Seng Hospital, ⁴Department of Respiratory and Critical Care Medicine, Changi General Hospital, ⁵Duke-NUS Graduate Medical School, Singapore, ⁶Department of Biological Sciences, National University Singapore, ⁷Universiti Kebangsaan Malaysia, Kuala Lumpur ⁸University of Dundee, Ninewells Hospital and Medical School, Dundee, Scotland.

Introduction

- Atopy and sensitization in respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF) are associated with poorer lung function and worse clinical outcomes¹⁻⁴. The role of atopy in non-CF bronchiectasis remains unexplored.

Aim

- We aim to determine the presence of atopy in two independent and geographically diverse cohorts of patients with non-CF bronchiectasis.

Methods

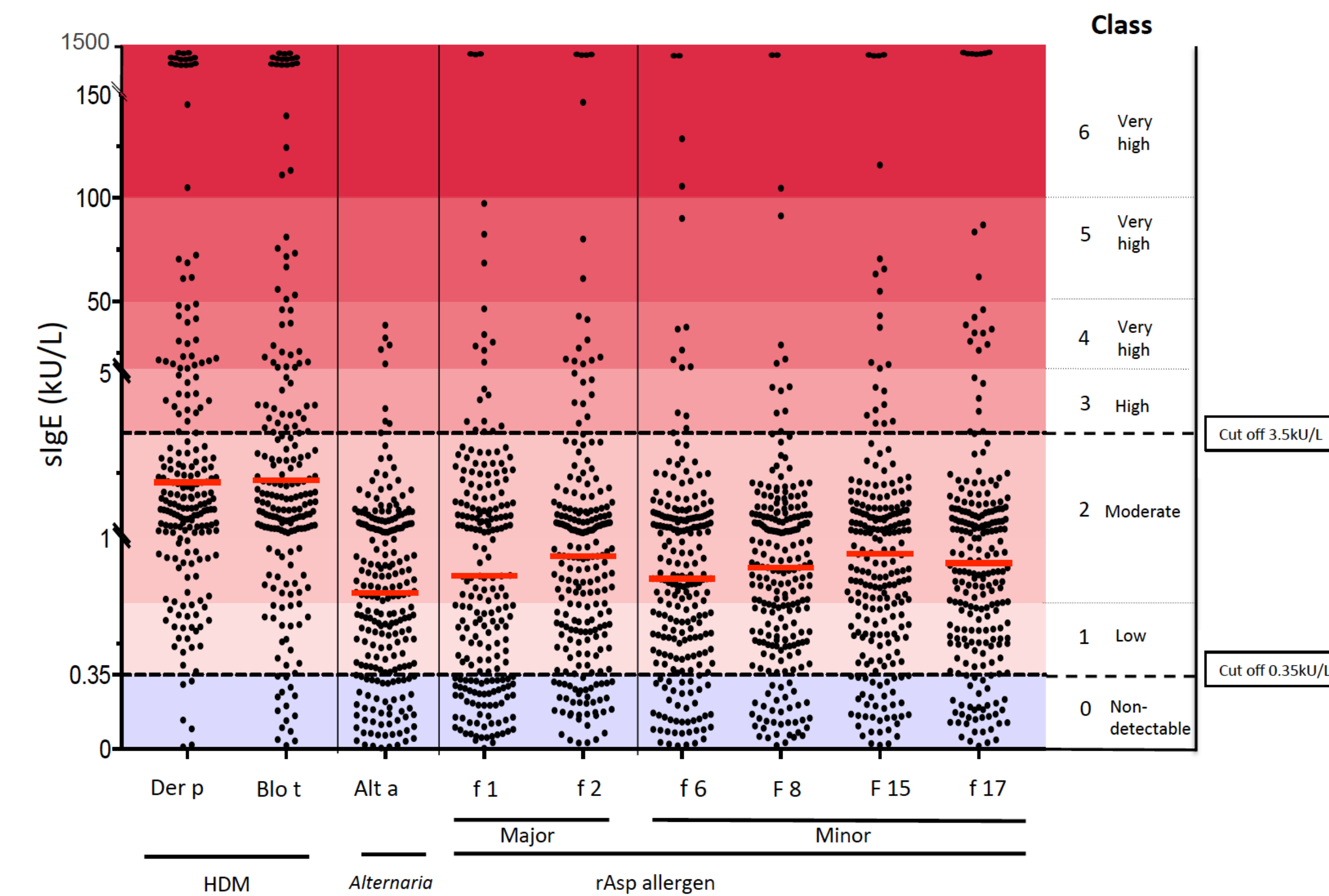
- 138 stable bronchiectasis patients across three different hospitals in Singapore (Singapore General Hospital, Changi General Hospital and Tan Tock Seng Hospital) and a single hospital in Malaysia (UKM, Medical Centre) were matched with 100 stable bronchiectasis patients from Ninewells Hospital, Dundee, United Kingdom.
- The cohorts were matched on age, gender and disease severity according to the Bronchiectasis Severity Index (BSI).
- Serum specific IgE (sIgE) titre against major inhalant allergen sources, including those from house dust mite (*Dermatophagoides pteronyssinus* [Der p], *Blomia tropicalis* [Blo t]), *Alternaria alternata* (Alt a), and recombinant *Aspergillus fumigatus* allergens (rAsp f) 1, 2 (major allergens), 6, 8, 15 and 17 (minor allergens), were measured and correlated with clinical outcomes, disease severity and pulmonary function.

Characteristic	Non-CF Bronchiectasis (n=238)	Asian Bronchiectasis (n=138)	Matched cohorts	
			Asian (n=100)	European (n=100)
Age : median (IQR)	68 (64-71)	65 (58-73)	65 (58-74)	69 (64-76)
Gender : n (%)				
Female	130 (55%)	77 (55%)	59 (59%)	53 (53%)
Male	108 (45%)	61 (45%)	41 (41%)	47 (47%)
Etiology n (%)				
Idiopathic	145 (61%)	85 (62%)	63 (63%)	60 (60%)
Post-infection	56 (23.5%)	43 (31%)	27 (27%)	27 (27%)
Other	37 (15.5%)	10 (7%)	10 (10%)	13 (13%)
BSI status : n (%)				
Severe	147 (62%)	84 (61%)	63 (63%)	63 (63%)
Moderate	71 (30%)	45 (33%)	26 (26%)	26 (26%)
Mild	20 (8%)	9 (6%)	11 (11%)	11 (11%)
BSI score : median (IQR)	9 (6-13)	10 (7-14)	10 (7-14)	9 (6-12)
BMI (kg/m ²) : median (IQR)	21 (18-27)	19 (17-22)	19 (17-22)	27 (22-31)
MRC dyspnea score : n (%)				
1-3	200 (84%)	121 (88%)	90 (90%)	79 (79%)
4	26 (11%)	10 (7%)	6 (6%)	16 (16%)
5	12 (5%)	7 (5%)	4 (4%)	5 (5%)
FEV ₁ % predicted	73.6(54-87)	69 (51-84)	68.5(52-84)	75.7(56.6-95.6)
Radiological severity : n (%)				
1-2 lobes involved	106 (45%)	62 (45%)	43 (43%)	44 (44%)
3 or more lobes involved	132 (55%)	76 (55%)	57 (57%)	56 (56%)
No. of exacerbations in previous year : n (%)				
0	84 (35%)	69 (50%)	44 (44%)	15 (15%)
1-2	82 (35%)	51 (37%)	41 (41%)	31 (31%)
3 or more	72 (30%)	18 (13%)	15 (15%)	54 (54%)
Hospital admissions before study : n (%)				
Yes	88 (37%)	63 (46%)	43 (43%)	25 (25%)
No	150 (63%)	75 (54%)	57 (57%)	75 (75%)
Colonization with other organisms : n (%)				
Yes	127 (53%)	60 (43%)	44 (44%)	67 (67%)
No	111 (47%)	78 (57%)	56 (56%)	33 (33%)
Pseudomonas colonisation : n (%)				
Yes	23 (10%)	18 (13%)	15 (15%)	5 (5%)
No	215 (90%)	120 (87%)	85 (85%)	95 (95%)

Table 1: Demographics of stable bronchiectasis patients comprising Asian and European matched cohorts

Results

Figure 1: High frequencies of sensitization to specific allergens of house dust mite (HDM), and recombinant *Aspergillus fumigatus* (rAsp) in non-CF bronchiectasis



Definition of abbreviation: Der p= *Dermatophagoides pteronyssinus*, Blo t= *Blomia tropicalis*; Alt a = *Alternaria alternata*, rAsp= recombinant *Aspergillus fumigatus*, sIgE= Specific immunoglobulin E, * p ≤ 0.05, **p ≤ 0.01.

Figure 2: Differing pattern of sensitization between Asian and European patients with stable non-CF bronchiectasis.

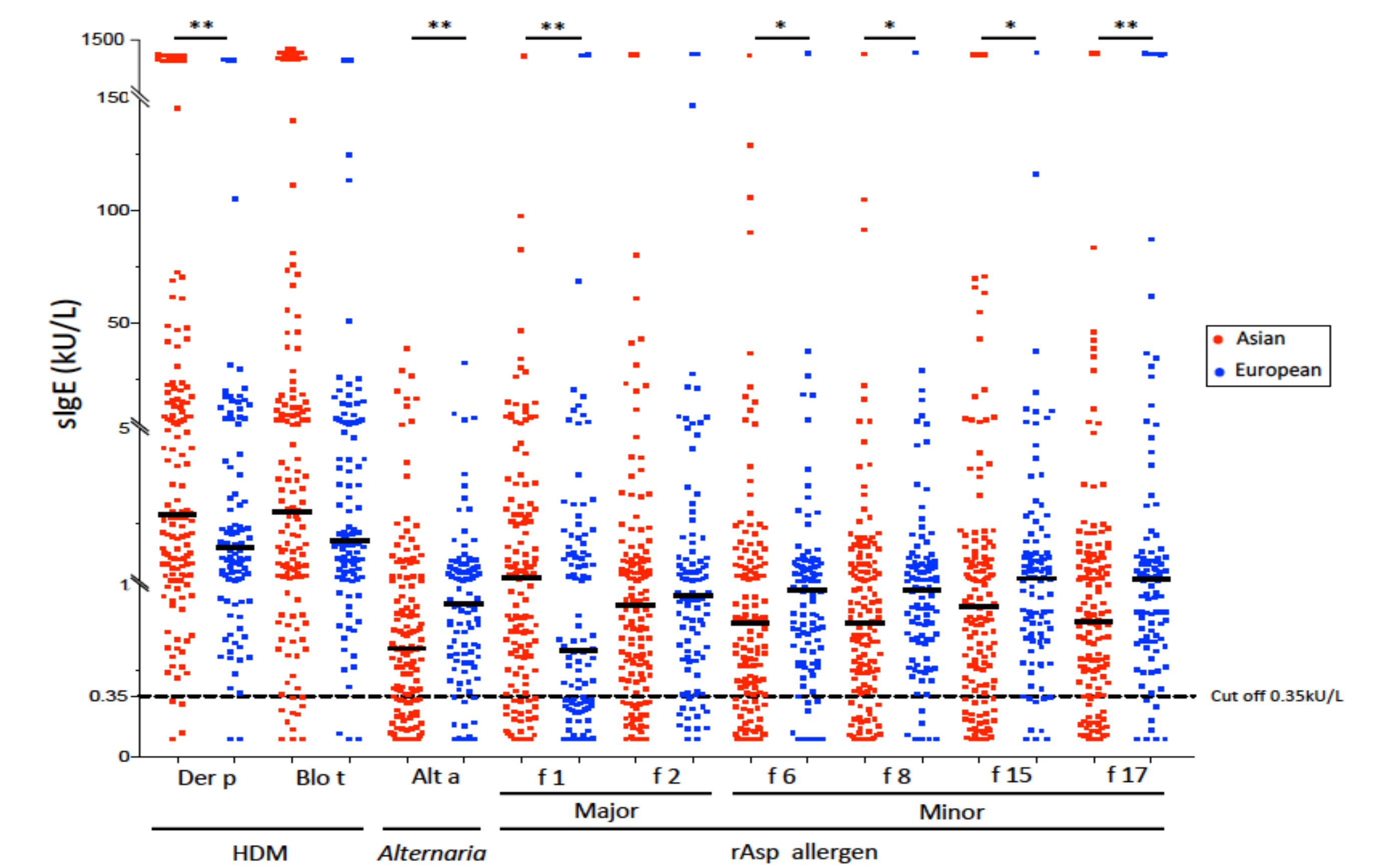


Table 2: sIgE titer and associations with clinical outcomes.

Allergen		Asian	European	Median FEV ₁						Median Exacerbations						sABPA n (%)						Effect on clinical outcome
				Asian			European			Asian			European			Asian			European			
				<3	≥3	p-value	<3	≥3	p-value	<3	≥3	p-value	<3	≥3	p-value	<3	≥3	p-value	<3	≥3	p-value	
House dust mite	Der p	↑↑	↑	76	61	0.039*	76.7	72.3	0.473	1	1	0.925	3	3	0.468	10 (13%)	12 (19%)	0.484	15 (21%)	6 (21%)	1	Decreased FEV ₁ , in Asians
	Blo t	↑	↑	75	61	0.04*	77.5	74.8	0.40	0	1	0.908	3	3	0.86	8 (12%)	14 (26%)	0.059	11 (18%)	10 (26%)	0.323	
<i>Alternaria</i>	Alt a	↑	↑↑	68	84	0.305	76.2	64.7	0.468	1	1	0.777	3	5	0.138	19 (15%)	3 (33%)	0.382	19 (20%)	2 (33%)	0.603	-
	Major	↑↑	↑	69	62	0.16	76.7	66.2	0.028*	1	0	0.407	3	1.5	0.394	17 (16%)	5 (17%)	0.782	19 (22%)	2 (17%)	1	Decreased FEV ₁ , in Europeans
<i>Aspergillus</i>	rAsp f1	↑↑	↑	69	66	0.484	76.7	66.9	0.174	0	1	0.617	3	3	0.463	17 (14%)	5 (31%)	0.137	16 (19%)	5 (36%)	0.164	
	rAsp f2	↑	↑↑	70	57	0.485	76.2	66.9	0.647	0	1	0.144	3	3.5	0.464	18 (14%)	4 (31%)	0.223	19 (21%)	2 (25%)	0.673	
	rAsp f6	↑	↑↑	70	56	0.182	76.2	75.2	0.927	0	1.5	0.308	3	1	0.423	18 (14%)	4 (40%)	0.054	20 (22%)	1 (10%)	0.684	
	rAsp f15	↑	↑↑	70	57	0.124	76.2	75.2	0.525	0	1	0.205	3	2	0.729	15 (13%)	7 (33%)	0.045*	16 (19%)	5 (36%)	0.164	
Minor	rAsp f17	↑	↑↑	69	65	0.834	77.5	68.9	0.162	0	1.5	0.035*	3	3	0.802	16 (13%)	6 (43%)	0.011*	16 (19%)	8 (47%)	0.008**	Increased exacerbations in Asians Increased in sABPA

↑ elevated sIgE titer, ↑↑ markedly elevated sIgE titer

Conclusion

- High frequencies of clinically significant (≥Class 3) atopy were detected in non-CF bronchiectasis, demonstrating geographic variation.
- Future work should address specific mechanisms driving this phenomenon.

References

- Warner JO, Taylor BW, Norman AP, Soothill JF. Association of cystic fibrosis with allergy. *Arch Dis Child* 1976; 51: 507-511.
- Wang J, Visness CM, Calatroni A, Gergen PJ, Mitchell HE, Sampson HA. Effect of environmental allergen sensitization on asthma morbidity in inner-city asthmatic children. *Clin Exp Allergy* 2009; 39: 1381-1389.
- Jamieson DB, Matsui EC, Belli A, McCormack MC, Peng E, Pierre-Louis S, Curtin-Brosnan J, Breyse PN, Diette GB, Hansel NN. Effects of allergic phenotype on respiratory symptoms and exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013; 188: 187-192.

Funding

This research is supported by the Singapore Ministry of Health's National Medical Research Council under its Transition Award (NMRC/TA/0048/2016) (S.H.C) and the Changi General Hospital Research Grant (CHF2016.03-P) (T.B.L.). C.F.T. has received research support from the Singapore Ministry of Education Academic Research Fund, the Singapore Immunology Network, and the Biomedical Research Council (BMRC) (N-154-000-038-001, R-154-000-404-112, R-154-000-553-112, R-154-000-565-112, R-154-000-630-112, R-154-000-A08-592, R-154-000-A27-597, SigN-06-006, SigN-08-020, BMRC/01/1/21/18/077, BMRC/04/1/21/19/315).