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Global ethnic and geographic differences in the clinical presentations of anti-neutrophil cytoplasm antibody–associated vasculitis

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Abstract

Objectives. There are few data on clinical profiles of ANCA-associated vasculitis (AAV) in different ethnic populations. The aim of this study was to examine the differences in the ANCA type and clinical features of AAV between populations using the Diagnostic and Classification Criteria in Vasculitis Study (DCVAS) dataset.

Methods. The DCVAS is an international, multicentre, observational study recruiting in 133 sites. Eight ethnic categories were analysed: Northern European, Caucasian American, Southern European, Middle Eastern/Turkish, Chinese, Japanese, Indian subcontinent and other. ANCA type was categorized as myeloperoxidase (MPO), PR3 and ANCA negative. Organ system involvement was recorded using a standard dataset. Differences were analysed by chi-squared tests using a Bonferroni correction and logistic regression (adjusting for age and sex). Northern European was the reference population.

Results. Data from 1217 patients with AAV were available and the 967 (79.5%) patients recruited by rheumatology departments were analysed to reduce confounding by recruitment specialty. There were differences in ANCA type between ethnic categories ($P < 0.001$): MPO-ANCA was more common than PR3-ANCA in Japanese, Chinese and Southern Europeans; PR3-ANCA was more common in the other groups. Compared with Northern Europeans, Japanese had a nearly 60-fold increased chance of having MPO-ANCA (*vs* PR3-ANCA) [odds ratio (OR) 59.2 (95% CI 8.0, 440.7), $P < 0.001$] and Chinese had a nearly 7-times increased chance [OR 6.8 (95% CI 2.6, 17.8), $P < 0.001$]. Ophthalmologic and otorhinolaryngologic involvement were less common in Japanese and Chinese populations than Northern Europeans; otherwise, there were few differences in organ involvement between ethnic groups.

Conclusion. This study confirms the previously observed differential occurrence of MPO-AAV and PR3-AAV between different ethnic groups.

Key words: ANCA-vasculitis, epidemiology, PR3-ANCA, MPO-ANCA

CLINICAL SCIENCE

Rheumatology key messages

- PR3-ANCA vasculitis is the predominant type of vasculitis in Northern Europeans, Middle Eastern/Turkish and people from the Indian subcontinent.
- MPO-ANCA vasculitis is the predominant subtype in Japanese and Chinese populations.
- MPO-AAV and PR3-ANCA-associated vasculitis occur with similar frequency in Caucasian Americans and Southern Europeans.

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Introduction

ANCA-associated vasculitis (AAV) is a group of conditions characterized by necrotizing vasculitis and the presence of ANCA in serum. The three types of AAV—granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis and microscopic polyangiitis (MPA)—are distinguished by their clinical features and ANCA type. Geoepidemiological data from Europe suggests that GPA is more common than MPA in Northern Europe, while the reverse is reported in Southern Europe [1, 2]. A comparative study between the UK and Japan observed that the overall incidence of AAV was similar but that MPA and myeloperoxidase (MPO)-positive AAV (MPO-AAV) was the predominant type in Japan (>80%) and PR3-positive AAV (PR3-AAV) was the predominant type in the UK (>60%) [3]. Case series from China suggest that MPA is more common than GPA [4]. In a multi-ethnic series from Chapel Hill, NC, USA, GPA was less common in African Americans [5]. Anecdotal evidence from European experts in vasculitis suggests that MPO-ANCA is more common in Southern Europe, while data from China suggests that MPO-ANCA is more common than PR3-ANCA [4].

The UK–Japan comparative study suggested that respiratory and otorhinolaryngologic involvement was less common in Japanese patients with AAV than in the UK; for the GPA subset, respiratory and renal involvement was less common in Japan [3]. A recent study of the clinical features of GPA patients in France noted that black patients (i.e. sub-Saharan and Afro-Caribbean) had more severe granulomatous manifestations and shorter time to relapse [6]. There are few comparative data on the clinical profiles of patients with AAV in other populations, particularly using clinical data collected globally with a standardized method.

The Diagnostic and Classification of Vasculitis (DCVAS) study is an international observational study with the aim of developing new classification criteria for AAV [7]. The dataset contains rich data on the clinical features of patients from many different countries and ethnic backgrounds. The goal of the present study was to investigate the hypothesis that there are differences in the clinical presentations of patients with AAV of different ethnicities.

Methods

The methodology for DCVAS has been described previously [7]. Patients used in this analysis were recruited into DCVAS between September 2014 and March 2016. We included patients with a diagnosis of AAV provided by their physician-investigators. As there are no published classification criteria for AAV, the DCVAS team validated the diagnosis of these patients using external expert review and this analysis demonstrated a high degree of agreement with the original diagnosis of AAV (DCVAS unpublished data). Data on ethnicity, age, sex, ANCA status (ANCA-PR3, ANCA-MPO positive, ANCA negative), specialty of the referring clinic and clinical features were extracted. Organ involvement at presentation was assessed using a standard form documenting the presence or absence of disease in 11 organ systems (general/constitutional, musculoskeletal, skin, ophthalmic, otorhinolaryngologic, respiratory, cardiac, gastrointestinal, genitourinary, renal and neurological).

Ethnicity was recorded by the referring physician in one of the following 19 groups: African North, African sub-Saharan, African American, Black Caribbean, Chinese Han, Chinese other, European North, European South, Indian subcontinent (Indian, Pakistani/Bangladeshi), Japanese, Korean, Latin American Native, Latin American Mestizo, Middle Eastern, Pacific Islander, Turkish, White Caucasian American and other. The study subdivided patients of European ethnicity into Northern and Southern. We based this subdivision on genetic studies of European population substructure, which suggest that there is a North–South genetic variation. Based on this we categorized patients from Spain, Italy, Greece and the Balkans as Southern European and patients from the UK, Ireland, the Nordic countries, the Benelux countries (Belgium, The Netherlands and Luxembourg), Estonia, Latvia and Lithuania, Slovakia, France, Germany, Austria and Poland as Northern Europeans [8]. Ethnicity was categorized for analysis into eight groups: Northern European, Caucasian American, Southern European, Middle Eastern/Turkish, Chinese, Japanese, Indian subcontinent and other. Patients with more than one ethnicity recorded were coded as other. Missing data were quantified and the one missing age value was imputed from the median for the cohort.

Age, sex and recruiting specialty were identified from the literature as likely to be associated with both ethnicity and our outcomes (ANCA type and clinical features) [2, 3] and these were considered a priori confounders. Age (continuous variable) and sex (binary variable) were adjusted for in the statistical analysis. However, with six specialties, and zero values for some specialties in some ethnic categories, statistical adjustment was not possible so the analysis was limited to only patients recruited from the largest recruiting specialty.

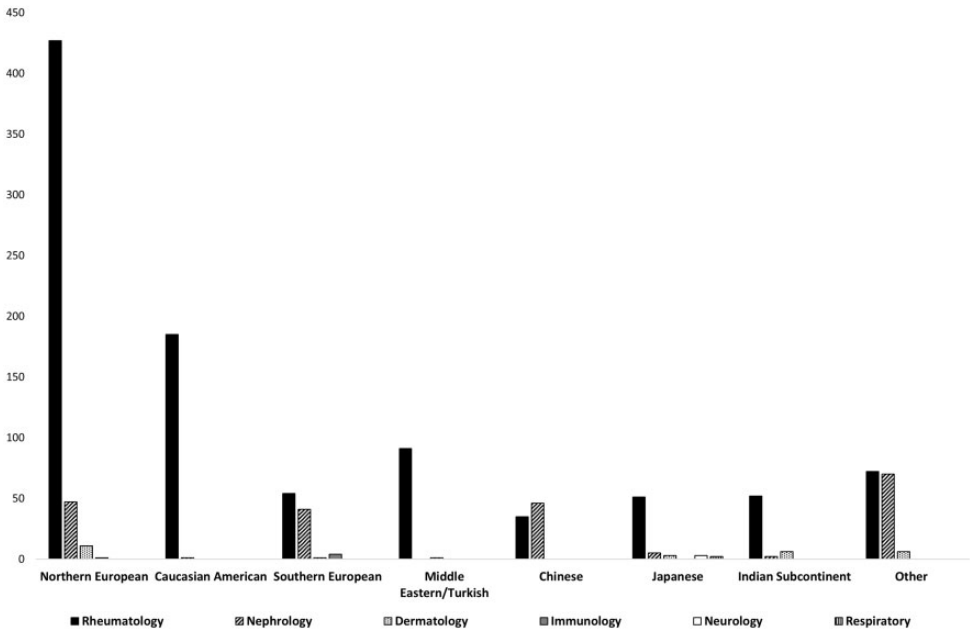
Ethical approval for the DCVAS study was obtained at all sites. Participants consented to the study and access to their records was granted. The procedures followed were in accordance with the ethical standards of the local responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983. No additional approval was required for this study.

Statistical analysis

We tested whether there were differences in the ANCA type (MPO-ANCA, PR3-ANCA or ANCA negative) of patients from each ethnic category using chi-squared tests of 8×3 contingency tables. We calculated the odds ratio (OR) for ANCA-negative compared with MPO/PR3-ANCA, and MPO-ANCA compared with PR3-ANCA in each ethnic category by logistic regression and then adjusted this for age and sex. Correction for multiple testing was done by the Bonferroni method using eight variables and accordingly we set the significance level at $P < 0.0063$.

We also investigated whether there were differences in the presence of symptoms in each organ system between

Fig. 1 Distribution of patients recruited by each specialty in each ethnic category



ethnic categories by chi-squared tests of 8 × 2 contingency tables. Correction for multiple testing was done by the Bonferroni method using 11 variables and accordingly we set the significance level at $P < 0.0045$. We calculated the OR for involvement of each organ system in each ethnic group using logistic regression with the European North ethnic category (the largest group) as the reference population and then adjusted this for age and sex. We also separately reported ethnic groups in which organ systems were affected ±2-fold as often as the reference (northern European) group (OR <0.5 or OR >2), so that large effects in small ethnic groups were not missed due to not reaching statistical significance because of their small sample size. Statistical analysis was carried out using STATA version 14 (StataCorp, College Station, TX, USA).

Results

We used the DCVAS dataset (as of 22 March 2016). There were 1217 patients who had a diagnosis of AAV and were included in the study. The largest recruiting specialty was rheumatology, which recruited 967 (79.5%) patients, 212 (17.4%) patients were recruited by nephrology clinics and a small number of patients were recruited from immunology, neurology, respiratory and dermatology clinics [totalling 38 (3.0%)]. There was differential recruitment between specialties; in northern Europe only 10% of patients were recruited from nephrology clinics, whereas in Chinese patients 60% were recruited from nephrology clinics (Fig. 1 and supplementary Table S1, available at *Rheumatology* Online). To control for this we chose to confine our analysis to patients recruited from rheumatology clinics. Table 1 gives the ethnicity breakdown, clinical diagnosis and ANCA status of both the whole cohort and the patients recruited from rheumatology. The median age of the patients recruited from rheumatology was 57.5 years [interquartile range (IQR) 45.2–67.6]. This was similar to the age distribution of the whole cohort [median 58.3 years (IQR 45.6–68.3)].

ANCA type

The frequency of PR3-ANCA varied between 61.2% in Northern Europeans and 2.1% in Japanese and the frequency of MPO-ANCA varied between 24.6% in Northern Europeans and 81.3% in Japanese (Table 2 and supplementary Fig. S1, available at *Rheumatology* Online). Compared with Northern Europeans, Japanese had a nearly 60-fold increased chance of having MPO-ANCA (rather than PR3-ANCA) [OR 59.2 (95% CI 8.0, 440.7), $P < 0.001$] and Chinese had a nearly 7-fold increased chance of having MPO-ANCA [OR 6.8 (95% CI 2.6, 17.8), $P < 0.001$]. There was also a significantly increased chance of having MPO-ANCA (rather than PR3-ANCA) compared with Northern Europeans in Caucasian Americans [OR 2.6 (95% CI 1.7, 4.0), $P < 0.001$] and Middle Eastern/Turkish [OR 2.3 (95% CI 1.3, 4.2), $P = 0.005$]; a similarly increased chance of MPO-ANCA (compared with PR3-ANCA) was found in Southern Europeans [OR 2.6 (95% CI 1.3, 5.0), $P = 0.006$], but this finding was not statistically significant.

The distribution of MPO- and PR3-ANCA in each ethnic group was similar in the whole sample of 1217 patients to that seen in the 967 recruited from rheumatology clinics (supplementary Figs S1–2, available at *Rheumatology* Online).

Table 1 Demographics, recruiting specialties, diagnoses and ANCA types of the cohort

Characteristic	All patients (n = 1217)	Patients from rheumatology (n = 967)
Sex, *n* (%)		
Male	594 (48.8)	487 (50.4)
Female	623 (51.2)	480 (49.6)
Ethnic category, *n* (%)		
European North	486 (39.9)	427 (44.2)
Caucasian American	186 (15.3)	185 (19.1)
European South	100 (8.2)	54 (5.6)
Middle Eastern/Turkish	92 (7.6)	91 (9.4)
Chinese	81 (6.7)	35 (3.6)
Japanese	64 (5.3)	51 (5.3)
Indian subcontinent	60 (4.9)	52 (5.4)
Other	148 (12.1)	72 (7.5)
Recruiting specialty, *n* (%)		
Rheumatology	967 (79.5)	967 (100)
Nephrology	212 (17.4)	
Immunology	28 (2.3)	
Neurology	5 (0.5)	
Respiratory	3 (0.3)	
Dermatology	2 (0.2)	
ANCA type, *n* (%)		
PR3	499 (41.0)	422 (43.6)
MPO	414 (34.0)	287 (29.7)
Negative	189 (15.0)	165 (17.1)
Other[a]	115 (8.5)	93 (9.6)

[a]This category either had not had their ANCA tested (n = 17), were both PR3 positive and MPO positive (n = 9) or only had ANCA found on immunofluorescence testing (n = 89).

The frequency of ANCA-negative AAV ranged between 14.2% in Northern Europeans and 33.3% in Chinese. In Caucasian Americans the frequency of ANCA-negative AAV was 25.3%, and this was statistically significantly higher than in Northern Europeans [OR 2.0 (95% CI 1.3, 3.2), P = 0.002]. In Chinese, the OR for ANCA-negative AAV compared with Northern Europeans was higher [OR 2.7 (95% CI 1.2, 5.9), P = 0.014], but this was not statistically significant.

Clinical profiles

In the rheumatology group, ophthalmologic, otorhinolaryngologic and renal involvement were significantly different among the ethnic categories (Table 3). Ophthalmologic involvement was 25 times less common in Japanese compared with Northern Europeans, and the effect remained reduced at 7 times less common in the MPO-ANCA subgroup, implying this difference was not driven entirely by the differences in predominant ANCA types. Otorhinolaryngologic involvement was five times less common in Japanese and half as common in Chinese compared with Northern Europeans. In the MPO-ANCA subgroup these effects reduced to 60% less common in Japanese and 40% less common in

Table 2 Distribution of ANCA types by ethnicity for the patients recruited in rheumatology clinics

Ethnicity	PR3	MPO	ANCA negative	Crude OR (95% CI), ANCA negative compared with MPO/PR3	Adjusted OR (95% CI)[a], ANCA negative compared with MPO/PR3	*P*-value	Crude OR (95% CI), MPO compared with PR3	Adjusted OR (95% CI)[a], MPO compared with PR3	*P*-value
Northern European	237 (61.2)	95 (24.6)	55 (14.2)	1	1		1	1	
Caucasian American	64 (37.7)	63 (37.1)	43 (25.3)	2.0 (1.3, 3.2)	2.0 (1.3, 3.2)	0.002*	2.5 (1.6, 3.7)	2.6 (1.7, 4.0)	<0.001*
Southern European	20 (37.0)	22 (40.7)	12 (22.2)	1.7 (0.9, 3.5)	1.8 (0.9, 3.7)	0.093	2.7 (1.4, 5.3)	2.6 (1.3, 5.0)	0.006
Middle Eastern/Turkish	38 (50.0)	25 (32.9)	13 (17.1)	1.2 (0.6, 2.4)	1.1 (0.6, 2.1)	0.794	1.6 (0.9, 2.9)	2.3 (1.3, 4.2)	0.005*
Chinese	7 (21.2)	15 (45.4)	11 (33.3)	3.0 (1.4, 6.6)	2.7 (1.2, 5.9)	0.014	5.3 (2.1, 13.5)	6.8 (2.6, 17.8)	<0.001*
Japanese	1 (2.1)	39 (81.3)	8 (16.7)	1.2 (0.5, 2.7)	1.6 (0.7, 3.7)	0.274	97.3 (13.2, 718.3)	59.2 (8.0, 440.7)	<0.001*
Indian subcontinent	26 (59.1)	11 (25.0)	7 (15.9)	1.1 (0.5, 2.7)	0.9 (0.4, 2.2)	0.818	1.1 (0.5, 2.2)	1.7 (0.8, 3.8)	0.174
Other	29 (46.8)	17 (27.4)	16 (25.8)	2.1 (1.1, 4.0)	1.8 (0.9, 3.4)	0.076	1.5 (0.8, 2.8)	1.9 (1.0, 3.8)	0.058

Table includes 874 patients with ANCA recorded; 93 either had not had their ANCA tested (n = 14), were both PR3 positive and MPO positive (n = 6) or only had ANCA found on immunofluorescence testing (n = 73). [a]Adjusted for age and sex. *Statistically significant using Wald's test at 0.0063 using a 95% significance level and the Bonferroni correction for testing eight variables.

Table 3 Involvement of organ systems by ethnicity for 967 patients with AAV recruited in rheumatology clinics

Organ System	Affected, *n* (%)	*P*-value	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Renal				
Northern European	115 (25.9)	0.001*	1	1
Caucasian American	32 (17.3)		0.6 (0.4, 0.9)	0.6 (0.4, 0.9)
Southern European	19 (35.2)		1.5 (0.8, 2.7)	1.4 (0.8, 2.6)
Middle Eastern/Turkish	35 (38.5)		1.7 (1.1, 2.7)	1.8 (1.1, 2.9)
Chinese	11 (31.4)		1.2 (0.6, 2.6)	1.3 (0.6, 2.8)
Japanese	21 (41.2)		1.9 (1.0, 3.5)	1.7 (0.9, 3.2)
Indian subcontinent	19 (36.5)		1.6 (0.9, 2.9)	1.8 (1.0, 3.3)
Other	25 (34.7)		1.4 (0.8, 2.5)	1.6 (0.9, 2.7)
Constitutional/general				
Northern European	350 (82.0)	0.074	1	1
Caucasian American	142 (76.8)		0.7 (0.5, 1.1)	0.7 (0.5, 1.1)
Southern European	36 (66.7)		0.4 (0.2, 0.8)	0.4 (0.2, 0.8)[b]
Middle Eastern/Turkish	79 (86.8)		1.4 (0.8, 2.8)	1.7 (0.9, 3.2)
Chinese	27 (77.1)		0.7 (0.3, 1.7)	0.8 (0.4, 1.9)
Japanese	39 (76.5)		0.7 (0.4, 1.4)	0.6 (0.3, 1.1)
Indian subcontinent	45 (86.5)		1.4 (0.6, 3.3)	1.8 (0.8, 4.2)
Other	57 (79.2)		0.8 (0.4, 1.6)	1.0 (0.5, 1.8)
Musculoskeletal				
Northern European	262 (61.4)	0.010	1	1
Caucasian American	97 (52.4)		0.7 (0.5, 1.0)	0.7 (0.5, 1.0)
Southern European	24 (44.4)		0.5 (0.3, 0.9)	0.5 (0.3, 0.9)
Middle Eastern/Turkish	59 (64.8)		1.2 (0.7, 1.9)	1.1 (0.7, 1.8)
Chinese	20 (57.1)		0.8 (0.4, 1.7)	0.8 (0.4, 1.6)
Japanese	22 (43.1)		0.5 (0.3, 0.9)	0.5 (0.3, 1.0)
Indian subcontinent	36 (69.2)		1.4 (0.8, 2.6)	1.3 (0.7, 2.4)
Other	46 (63.9)		1.1 (0.7, 1.9)	1.0 (0.6, 1.8)
Skin				
Northern European	133 (31.2)	0.354	1	1
Caucasian American	68 (36.8)		1.3 (0.9, 1.8)	1.3 (0.9, 1.9)
Southern European	18 (33.3)		1.1 (0.6, 2.0)	1.1 (0.6, 2.1)
Middle Eastern/Turkish	33 (36.3)		1.3 (0.8, 2.0)	1.1 (0.7, 1.8)
Chinese	11 (31.4)		1.0 (0.5, 2.1)	0.9 (0.4, 2.0)
Japanese	17 (33.3)		1.1 (0.6, 2.0)	1.3 (0.7, 2.5)
Indian subcontinent	21 (40.4)		1.5 (0.8, 2.7)	1.3 (0.7, 2.3)
Other	33 (45.8)		1.9 (1.1, 3.1)	1.7 (1.0, 2.9)
Ophthalmic				
Northern European	125 (29.3)	<0.001*	1	1
Caucasian American	42 (22.7)		0.7 (0.5, 1.1)	0.7 (0.5, 1.1)
Southern European	12 (22.2)		0.7 (0.4, 1.4)	0.7 (0.4, 1.4)
Middle Eastern/Turkish	20 (22.0)		0.7 (0.4, 1.2)	0.6 (0.4, 1.1)
Chinese	9 (25.7)		0.8 (0.4, 1.8)	0.8 (0.4, 1.7)
Japanese	1 (2.0)		0.04 (0.0, 0.4)	0.05 (0.0, 0.4) [b]
Indian subcontinent	24 (46.2)		2.1 (1.2, 3.7)	1.8 (1.0, 3.3)
Other	28 (38.9)		1.5 (0.9, 2.6)	1.4 (0.8, 2.4)
Otorhinolaryngologic				
Northern European	306 (71.7)	<0.001*	1	1
Caucasian American	135 (73.0)		1.1 (0.7, 1.6)	1.1 (0.7, 1.6)
Southern European	32 (59.3)		0.6 (0.3, 1.0)	0.6 (0.3, 1.1)
Middle Eastern/Turkish	60 (65.9)		0.8 (0.5, 1.2)	0.6 (0.4, 1.0)
Chinese	19 (54.3)		0.5 (0.2, 0.9)	0.4 (0.2, 0.8) [b]
Japanese	18 (35.3)		0.2 (0.1, 0.4)	0.3 (0.2, 0.5) [b]
Indian subcontinent	36 (69.2)		0.9 (0.5, 1.7)	0.6 (0.3, 1.2)
Other	49 (68.1)		0.8 (0.5, 1.4)	0.7 (0.4, 1.2)
Respiratory				
Northern European	278 (65.1)	0.59	1	1
Caucasian American	124 (67.0)		1.1 (0.8, 1.6)	1.1 (0.8, 1.6)
Southern European	35 (64.8)		1.0 (0.5, 1.8)	1.0 (0.5, 1.8)
Middle Eastern/Turkish	66 (72.5)		1.4 (0.9, 2.3)	1.4 (0.9, 2.4)

(continued)

TABLE 3 Continued

Organ System	Affected, *n* (%)	*P*-value	Crude OR (95% CI)	Adjusted OR (95% CI)[a]
Chinese	25 (71.4)		1.3 (0.6, 2.9)	1.4 (0.6, 2.9)
Japanese	32 (62.8)		0.9 (0.5, 1.6)	0.9 (0.5,1.6)
Indian subcontinent	40 (76.9)		1.8 (0.9, 3.5)	1.9 (0.9, 3.7)
Other	51 (70.8)		1.3 (0.8, 2.2)	1.4 (0.8, 2.4)
Cardiac				
Northern European	68 (15.9)	0.032	1	1
Caucasian American	39 (21.1)		1.4 (0.9, 2.2)	1.4 (0.9,2.2)
Southern European	6 (11.1)		0.7 (0.3, 1.6)	0.7 (0.3, 1.6)
Middle Eastern/Turkish	6 (6.6)		0.4 (0.2, 0.9)	0.4 (0.2, 0.9) [b]
Chinese	7 (20.0)		1.3 (0.6, 3.1)	1.3 (0.6, 3.1)
Japanese	10 (19.6)		1.3 (0.6, 2.7)	1.3 (0.6, 2.8)
Indian subcontinent	4 (7.7)		0.4 (0.2, 1.3)	0.4 (0.2, 1.3) [b]
Other	15 (20.8)		1.4 (0.7, 2.6)	1.4 (0.7, 2.6)
Gastrointestinal				
Northern European	84 (19.7)	0.203	1	1
Caucasian American	41 (22.2)		1.2 (0.8, 1.8)	1.2 (0.8, 1.8)
Southern European	8 (14.8)		0.7 (0.3, 1.6)	0.7 (0.3, 1.6)
Middle Eastern/Turkish	19 (20.9)		1.1 (0.6, 1.9)	1.0 (0.6, 1.8)
Chinese	9 (25.7)		1.4 (0.6, 3.1)	1.4 (0.6, 3.1)
Japanese	7 (13.7)		0.6 (0.3, 1.5)	0.7 (0.3, 1.6)
Indian subcontinent	15 (28.9)		1.7 (0.9, 3.2)	1.6 (0.8, 3.1)
Other	22 (30.6)		1.8 (1.0, 3.1)	1.8 (1.0, 3.1)
Genitourinary				
Northern European	50 (11.7)	0.018	1	1
Caucasian American	17 (9.2)		0.8 (0.4, 1.4)	0.8 (0.4, 1.4)
Southern European	2 (3.7)		0.3 (0.1, 1.2)	0.3 (0.1, 1.2) [b]
Middle Eastern/Turkish	8 (8.8)		0.7 (0.3, 1.6)	0.8 (0.4, 1.7)
Chinese	1 (2.8)		0.2 (0.0, 1.7)	0.2 (0.0, 1.7) [b]
Japanese	10 (19.6)		1.8 (0.9, 3.9)	1.7 (0.8, 3.6)
Indian subcontinent	10 (19.2)		1.8 (0.8, 3.8)	2.1 (0.9, 4.5)
Other	13 (18.1)		1.7 (0.9, 3.2)	1.8 (0.9, 3.6)
Neurological				
Northern European	164 (38.4)	0.562	1	1
Caucasian American	82 (44.3)		1.3 (0.9, 1.8)	1.3 (0.9, 1.8)
Southern European	23 (42.6)		1.2 (0.7, 2.1)	1.1 (0.6, 2.0)
Middle Eastern/Turkish	31 (34.1)		0.8 (0.5, 1.3)	0.9 (0.6, 1.5)
Chinese	12 (34.3)		0.8 (0.4, 1.7)	0.9 (0.4, 1.9)
Japanese	22 (43.1)		1.2 (0.7, 2.2)	1.0 (0.6, 1.9)
Indian subcontinent	24 (46.2)		1.4 (0.8, 2.5)	1.6 (0.9, 3.0)
Other	33 (45.8)		1.4 (0.8, 2.2)	1.5 (0.9, 2.5)

[a]Adjusted for age and sex. [b]Estimated organ involvement ±2-fold difference from the reference (Northern European) group. *Statistically significant at 0.0045 using a 95% significance level and the Bonferroni correction for testing 11 variables.

Chinese, again suggesting an effect of ethnicity that is in addition to the influence of ANCA type. Renal involvement was less common in Caucasian Americans [OR 0.6 (95% CI 0.4, 0.9)] and more common in the Middle Eastern/Turkish [OR 1.8 (95% CI 1.1, 2.9)] and Indian/Pakistani/Bangladeshi [OR 1.8 (95% CI 1.0, 3.3)] categories compared with Northern Europeans.

Although overall the differences in the distribution of general/constitutional, cardiac and genitourinary organ systems were not significant, some small ethnic groups showed rates of involvement that were more than ±2-fold that found in Northern Europeans. These included constitutional/general symptoms were less common in Southern Europeans [OR 0.4 (95% CI 0.2, 0.8)], cardiac involvement was less common in Middle Eastern/Turkish [OR 0.4 (95% CI 0.2, 0.9)] and people from the Indian subcontinent [OR 0.4 (95% CI 0.2, 1.3)] and genitourinary involvement was less common in Southern Europeans [OR 0.3 (95% CI 0.1, 1.2)] and Chinese [OR 0.2 (95% CI 0.0, 1.7)].

Results for the whole sample of 1217 patients and the subgroup of 212 patients recruited by nephrology clinics are shown in supplementary Table S2, available at *Rheumatology* Online, for comparison.

Discussion

In this study we have compared for the first time the clinical presentations and ANCA status of patients with AAV in a large (1217 patient) multinational cohort using a standardized assessment. This is one of the largest cohorts of AAV patients assembled. The main findings of this analysis are that MPO-AAV is the predominant subtype of

AAV in the Japanese group, where it comprises 81.3% of AAV, and in the Chinese group, where it comprises 45.4% of AAV, which is not the same pattern as is found in Northern Europeans. This difference was the same in the whole cohort as in the rheumatology patients. In our analysis there were few significant differences in the clinical profiles of patients of different ethnicities.

The major strength of this study is the widespread international recruitment, with patients being recruited from 133 centres in 33 countries, together with the standardized collection of clinical data. This has enabled us to compare the clinical features and ANCA status across different ethnicities and countries. We have applied stringent criteria for significance testing with correction for multiple comparisons and thus we are only reporting differences with strong effects.

The main limitation of this type of study is the potential for selection bias. The patients who are included may not be representative of all patients of that ethnicity, meaning either spurious associations may be reported or true associations may not be found. We had also been concerned that differences in ANCA types and clinical features of patients would occur between those recruited from different specialties, such as the differences in ANCA types and clinical features between patients presenting to nephrology and rheumatology services [9]. Because each specialty did not recruit an equal proportion of patients from each ethnicity, we limited our main analysis to patients recruited only by the largest recruiting specialty (rheumatology). This reduced the impact of this bias while only slightly reducing the power of our study to detect differences and reducing the sample size from 1217 to 967. Previous studies have not addressed this issue [3, 4].

The other main limitation is a problem inherent in the study of rare diseases. Despite recruiting $>$1000 patients, there remained small numbers of patients in some subgroups, which meant that we were unable to perform a separate analysis for PR3-AAV and MPO-AAV, and differences in some smaller ethnic groups had large effect sizes (more than ±2-fold difference from the Northern European reference group) but were not statistically significant. Therefore, in addition to results that are statistically significant, we have reported results that estimate a more than ±2-fold difference from the Northern European reference group, as these could be clinically relevant.

The observed differences in MPO-AAV and PR3-AAV between Northern Europe, Southern Europe, Japan and China could represent the effect of different genetic backgrounds. HLA-DPB1*0401 is the major HLA susceptibility allele for GPA in European populations, but shows major variation worldwide [10, 11]. There is a fairly consistent allele frequency in Europe of ~0.36–0.47. The allele is much less frequent in Japan (0.050) and China (0.095, Han Cantonese), two populations in this study in which PR3-AAV is less common. In a small population of Han Chinese, PR3-AAV was associated with DRB1*1202, which is relatively more common in that population than in Europe [12]. The two major non-HLA-associated single nucleotide polymorphisms in a genome-wide association study (GWAS) were *SERPINA1* and *PRTN3*. *SERPINA1* encodes alpha-1 antitrypsin. Haplotype analysis suggests that the causal variant is either the Z allele or in close linkage disequilibrium with it [11]. The PI*Z allele of the alpha-1 antitrypsin gene shows widespread variation in its geo-epidemiology [13], but its frequency does not appear to parallel that of GPA [14]. There are presently insufficient data on the occurrence of *PRTN3* (which encodes the *PR3* gene) to determine whether its frequency mirrors that of GPA. The genetic background of MPA is less well known. However, it clearly has a different HLA background; in the European GWAS HLA-DPB1*0401 was not associated with MPA or MPO-ANCA vasculitis, but with HLA-DQ [11, 15]. In Japanese populations, DRB1*0901 and DQB1*03:03 are associated with MPA- and MPO-AAV and are among the most frequent HLA class II haplotypes in East Asian populations; these haplotypes are rare in populations of European and African ancestry [16].

Conclusions

In this global study of the clinical features of AAV, we have shown that PR3-AAV is the predominant type of vasculitis in Northern Europeans, Middle Eastern/Turkish and people from the Indian subcontinent, while MPO-AAV is the predominant type of vasculitis in Japanese and Chinese populations. MPO-AAV and PR3-AAV occur with similar frequency in Caucasian Americans and Southern Europeans. Apart from the reduced occurrence of otorhinolaryngologic and ophthalmological involvement in Chinese and Japanese populations, we demonstrated few differences in the clinical presentations of AAV in different ethnic groups. In the context of such a rare disease, the large number of patients included in this study represents hugely successful collaboration.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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