Journal of Human Genetics (2018) 63:55–62
https://doi.org/10.1038/s10038-017-0362-2

ARTICLE

Association of *ETS1* polymorphism with granulomatosis with polyangiitis and proteinase 3-anti-neutrophil cytoplasmic antibody positive vasculitis in a Japanese population

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Received: 18 July 2017 / Revised: 10 August 2017 / Accepted: 22 August 2017 / Published online: 5 October 2017

Abstract

ETS proto-oncogene 1, transcription factor (ETS1) is involved in various immune responses. Genome-wide association studies on systemic lupus erythematosus in Chinese populations identified the association of *ETS1* polymorphism in 3′ untranslated region, rs1128334A, which was associated with lower *ETS1* expression. In view of substantial sharing of susceptibility genes across multiple autoimmune diseases, we examined whether *ETS1* is associated with a rare autoimmune rheumatic disease, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Association of rs1128334 was tested in 466 Japanese patients with AAV and 1099 healthy controls by logistic regression analysis under the additive model. AAV patients were classified into 285 microscopic polyangiitis (MPA), 92 granulomatosis with polyangiitis (GPA), 56 eosinophilic GPA, and 33 unclassifiable AAV, according to the European Medicines Agency (EMEA) algorithm. Among the patients, 376 were positive for MPO–ANCA and 62 for PR3–ANCA. When the patients were classified according to the EMEA classification, rs1128334A allele was significantly increased in GPA ($P = 0.0060$, $P_c = 0.030$, odds ratio (OR), 1.54; 95% confidence interval (CI), 1.13–2.10). With respect to the ANCA specificity, significant association was observed in PR3–ANCA positive AAV ($P = 0.0042$, $P_c = 0.021$, OR, 1.72; 95% CI, 1.19–2.49). In conclusion, *ETS1* polymorphism was suggested to be associated with GPA and PR3–ANCA positive AAV in a Japanese population.

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of rare systemic vasculitides characterized by production of ANCA. AAV is classified into three subsets, microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA) based on clinical symptoms. Major ANCA antigens are myeloperoxidase (MPO) and proteinase 3 (PR3), and generally, MPO–ANCA is preferentially detected in MPA and EGPA, while PR3–ANCA is mainly observed in GPA [1].

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Prevalence of AAV subsets substantially differs between European and Japanese populations. In contrast to the European populations where GPA and PR3–ANCA positive AAV (PR3–AAV) account for the majority of AAV, MPA, and MPO–ANCA positive AAV (MPO–AAV) are predominant in Japan. According to the population-based prospective study, annual incidence of MPA and GPA are 18.2 and 2.1/million in Japan, while 6.5 and 14.3/million in the United Kingdom, respectively [2]. In addition, about half of the Japanese GPA patients are positive for MPO–ANCA [3]. Such epidemiological differences may partly be caused by differences in the genetic background between the populations of European and Asian ancestries.

Thus far, we reported association of *HLA-DRB1*09:01* and *DRB1*13:02* with susceptibility and protection to MPO–AAV, respectively, in a Japanese population [4]. On the other hand, *DPB1*04:01*, previously shown to be associated with GPA in populations of European ancestry

Table 1 Patients with AAV and healthy controls examined in this study

	Number	(%)[a]	Female/male	MPO–ANCA positive	PR3–ANCA positive
AAV patients	466		277/189	376	62
EMEA classification					
GPA	92	(19.7)	50/42	47	46
MPA	285	(61.2)	172/113	273	10
EGPA	56	(12.0)	35/21	28	4
Unclassifiable	33	(7.1)	20/13	28	2
Healthy controls	1099		789/310	N/A	N/A

N/A not available

[a]Percentage of the number of patients in each patient group among all AAV patients

[5], showed a tendency toward association with PR3–AAV also in Japan [4]. Of interest, *DRB1*09:01* is highly prevalent in the Japanese population (15.3%) [4], while very rare in the European populations (1.0%) (allele frequency net database; http://www.allelefrequencies.net) [6]. In contrast, *DPB1*04:01* is prevalent in the European populations (42.5%) (allele frequency net database) [6], but relatively rare in the Japanese (6.3%) [4]. These findings indeed support the hypothesis that differences in the genetic background may partly account for the differences in the incidence of AAV subsets between populations.

Recently, three genome-wide association studies (GWAS) of AAV have been published in the populations of European ancestry [7–9]. These studies, along with previous candidate gene studies [5, 10], demonstrated association of *HLA-DPB1*04* and *SERPINA1*, encoding α1-antitrpsin, with GPA or PR3–AAV, and also suggested several other candidate genes. However, with respect to MPA/MPO–AAV, convincing association was only reported in the *HLA-DR/DQ* region [7, 9]. This may partly be caused by relatively small sample size of MPA/MPO–AAV in the Caucasian studies. Thus, AAV genetics in Asian populations might provide valuable insights.

Due to the low prevalence of AAV, GWAS has not been reported in the Asian populations, and at this point, efficient selection of candidate genes is considered a reasonable approach. Recent studies have revealed that a number of susceptibility genes are shared across multiple autoimmune diseases [11]. Indeed, genes such as *IRF5*, *STAT4*, *BLK*, and *TNFAIP3* have been shown to be associated with systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and systemic sclerosis (SSc) in a Japanese population [12–15]. With respect to *HLA* risk or protective alleles in AAV, *DRB1*09:01* has been shown to be positively associated with SLE, RA, and type 1 diabetes [16, 17], while *DRB1*13:02* is associated with protection against SLE, RA, and SSc as well [18–20].

ETS proto-oncogene 1, transcription factor (ETS1) is a transcription factor belonging to the ETS family characterized by an ETS DNA-binding domain, which recognizes a GGAA/T motif [21]. ETS1 plays a role in immunity, angiogenesis, and cancer progression, and is expressed in B cells, T cells, natural killer cells, endothelial cells, and cancer cells [21–23]. ETS1 negatively regulates B-cell differentiation into plasma cells by suppressing function of BLIMP1, a positive regulator of plasma cell differentiation. In T cells, reduction of T helper (Th) 1 cytokine, interferon γ, and decrease in regulatory T cells (Tregs) were observed in *Ets1*-deficient mice. On the other hand, Th17 differentiation was enhanced by *Ets1* deficiency [22, 23].

GWAS on SLE in Chinese populations identified the association of two *ETS1* single nucleotide polymorphisms (SNPs) in tight linkage disequilibrium (LD), rs1128334 and rs6590330 [24, 25], which was later replicated in the European populations [26]. The SNP rs1128334 is located in 3′ untranslated region (UTR) of *ETS1* gene, and the SLE risk allele, rs1128334A, was reported to be associated with reduced *ETS1* expression [25]. In addition, association with rs1128334A was also observed in another rheumatic disease, ankylosing spondylitis (AS), in a Chinese population [27].

Based on the functional relevance of *ETS1* in AAV and previous reports of association with multiple rheumatic disease especially in the Asian populations, we considered *ETS1* as a candidate gene for AAV. Thus far, the association study of *ETS1* has not been reported in AAV in the Asian populations. In the present study, we investigated whether *ETS1* polymorphism is associated with AAV in a Japanese population.

Materials and Methods

Patients and healthy controls

Four hundred and sixty-six Japanese patients with AAV and 1099 healthy controls were studied. The patients were recruited at the institutes participating in the Research Committee on Intractable Vasculitides and in the Research Group on Progressive Renal Diseases, both organized by

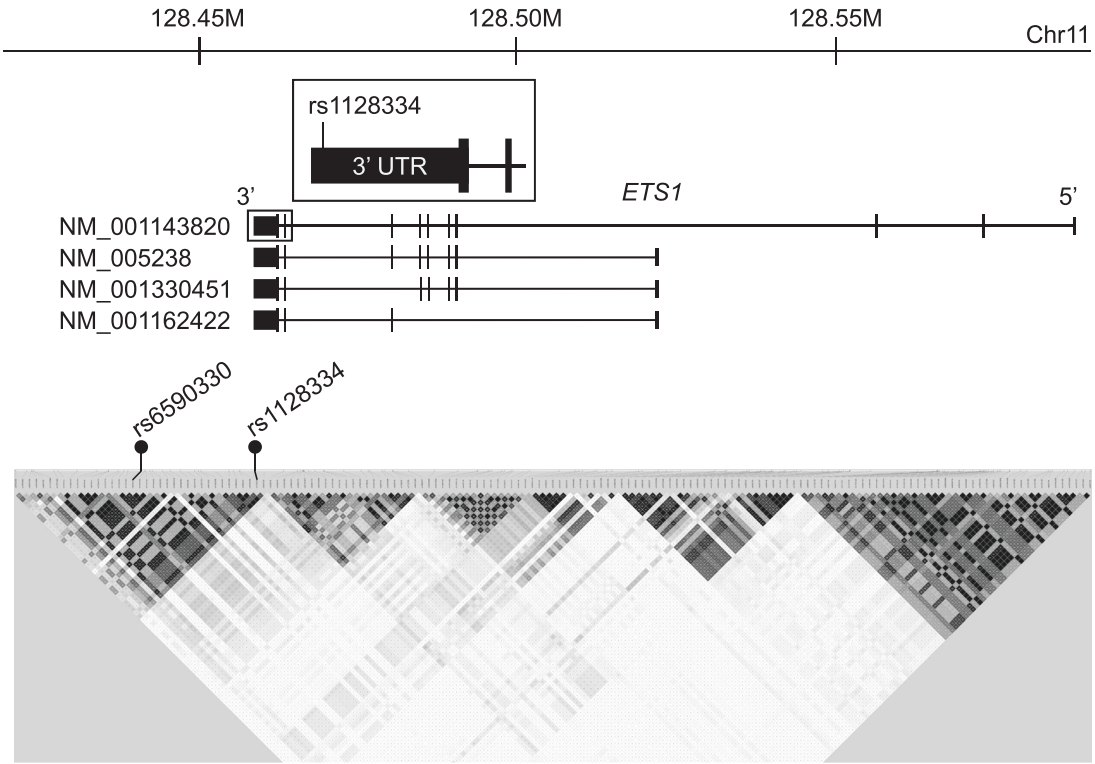

Fig. 1 Structure and linkage disequilibrium status of *ETS1* gene. Upper panel, four dominant *ETS1* splicing isoforms (RefSeq accession numbers: NM_001143820, NM_005238, NM_001330451, and NM_001162422). Inset shows the enlarged view of the position of rs1128334 in the 3′ UTR of *ETS1*. Lower panel, linkage disequilibrium plot in the *ETS1* region drawn using pairwise r^2 values between SNPs with minor allele frequency >0.2. SLE associated SNPs, rs1128334 and rs6590330, are indicated

the Ministry of Health, Labor, and Welfare of Japan, research groups organized by Sagamihara Hospital, National Hospital Organization, and the Tokyo Medical and Dental University. Healthy controls were recruited at University of Tsukuba, the University of Tokyo, Juntendo University, and Sagamihara Hospital. In addition, genomic DNA from 514 healthy individuals were purchased from the Health Science Research Resources Bank (Osaka, Japan).

The AAV patients were classified according to the European Medicines Agency (EMEA) algorithm (285 MPA, 92 GPA, 56 EGPA, and 33 unclassifiable) [28] or ANCA specificity (376 MPO–ANCA positive, 62 PR3–ANCA positive). Characteristics in the AAV patients and healthy controls are shown in Table 1. Forty-six patients were PR3–ANCA positive GPA, which accounts for 50% of GPA, and 74% of PR3–ANCA positive AAV.

Ethics statement

This study was reviewed and approved by the Ethics Committees of University of Tsukuba, National Hospital Organization Sagamihara Hospital, the Tokyo Medical and Dental University, Okayama University, Kyoto University, Kagawa University, Juntendo University, St. Marianna University, Kanazawa University, the University of Tokyo, Kyorin University, Saitama Medical Center Hospital, the University of Miyazaki, Toho University, Kobe University Hospital, Kitano Hospital, Shimane University, Nagoya City University, Ehime University, Jichi Medical University, Kyoto Prefectural University, Tokyo Medical University Hachioji Medical Center, Kitasato University Hospital, Hamamatsu University, National Hospital Organization Shimoshizu National Hospital, Tenri Hospital, Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, Hyogo University, Kawasaki Municipal Hospital, Sendai Shakaihoken Hospital, Tokyo Women's Medical College, Kyoundo Hospital, Tokyo Metropolitan Komagome Hospital, Ome Municipal General Hospital, Teikyo University, Hokkaido University, Fukuoka University, Okayama Saiseikai General Hospital, Aichi Medical University, Asahikawa Medical University, Kyushu University, Iwate Prefectural Central Hospital, and Nagasaki University. Written informed consent was obtained from all participants, except for some healthy individuals who donated blood for use in medical genetics studies before 2001, that is, prior to the implementation by the Japanese government of the Ethics Guidelines for Human Genome/Gene Analysis Research. From such healthy individuals, verbal informed consent for the genetics study had

Table 2 Association of *ETS1* polymorphism with AAV subsets in a Japanese population

ETS1 rs1128334	A/A	A/G	G/G	A	P	P_c[a]	OR	(95% CI)	Power[b]
AAV patients									
EMEA classification									
GPA	20 (0.217)	50 (0.543)	22 (0.239)	90 (0.489)	**0.0060**	**0.030**	**1.54**	**(1.13–2.10)**	0.798
MPA	53 (0.186)	138 (0.484)	94 (0.330)	244 (0.428)	0.072	0.36	1.19	(0.98–1.44)	0.445
EGPA	7 (0.125)	30 (0.536)	19 (0.339)	44 (0.393)	0.90	1.0	1.03	(0.69–1.52)	0.053
ANCA specificity									
PR3–AAV	17 (0.274)	30 (0.484)	15 (0.242)	64 (0.516)	**0.0042**	**0.021**	**1.72**	**(1.19–2.49)**	0.832
MPO–AAV	68 (0.181)	188 (0.500)	120 (0.319)	324 (0.431)	0.032	0.16	1.20	(1.02–1.43)	0.565
Healthy controls	156 (0.142)	539 (0.490)	404 (0.368)	851 (0.387)					

Significant association is shown in bold

OR odds ratio, *CI* confidence interval

[a]*P* values adjusted for multiple comparisons by Bonferroni correction

[b]Power to detect statistical association at the significance level of 0.05 under the log-additive model

been obtained. In accordance with the Japanese Ethical Guidelines for Human Genome/Gene Analysis Research, such samples were anonymized in an unlinkable fashion, and were included in this study after review and approval by the Ethics Committee of the University of Tsukuba. This study was conducted according to the principles expressed in the Declaration of Helsinki.

Genotyping

Genotypes of SNP rs1128334 were determined by the TaqMan SNP Genotyping Assays (Assay ID: C___7539918_10) (Thermo Fisher Scientific Inc, Waltham, MA).

Statistical analysis

Association was tested by logistic regression analysis under the additive model using Ekuseru-Toukei 2012 (Social Survey Research Information Co., Ltd., Tokyo, Japan). The significance level was set at 0.05. *P* values corrected for multiple testing by Bonferroni correction (P_c) were calculated by multiplying uncorrected *P* values by the number of tests ($n = 5$). Adjustment for gender difference between patients with each AAV subset and healthy controls was performed by conditional logistic regression analysis. Power to detect statistical association at the significance level of 0.05 was calculated under the log-additive model using Quanto version 1.2.4 (http://biostats.usc.edu/Quanto.html). Sample size of each subset and healthy controls and observed odds ratio in each comparison were employed for power calculation.

For the calculation of LD values, genotype data of the polymorphisms in the *ETS1* region was obtained from the 1000 Genomes browser (https://www.ncbi.nlm.nih.gov/variation/tools/1000genomes/), and r^2 values were calculated using Haploview version 4.0 software (Broad Institute, Cambridge, MA).

Genetic interaction between *ETS1* rs1128334 and *HLA-DPB1*04:01* was examined by logistic regression analysis as previously described [29]. The logistic regression model for interaction between gene i and gene j was defined as follows: $\mathrm{logit}(P) = \beta_0 + \beta_i x_i + \beta_j x_j + \beta_{ij} x_i x_j$, where x_i and x_j are 2 for the homozygotes for the risk alleles, 1 for the heterozygotes, and 0 for homozygotes for non-risk alleles, respectively. rs1128334A and *HLA-DPB1*04:01* were risk alleles for *ETS1* and *HLA-DPB1*.

Results

ETS1 gene is located on chromosome 11q24.3 and several *ETS1* splicing isoforms were reported, among which four representative isoforms are shown in Fig. 1. LD analysis was conducted using the HapMap JPT (Japanese in Tokyo) data obtained from the 1000 Genomes browser. The SNPs associated with susceptibility to SLE, rs1128334 and rs6590330, are located in *ETS1* 3′ UTR and downstream of *ETS1*, respectively. These SNPs are in almost absolute LD ($r^2 = 0.96$). Therefore, rs1128334 in *ETS1* 3′ UTR was analyzed as the tag SNP in this study.

First, to examine whether *ETS1* rs1128334 is associated with AAV subsets based on EMEA classification (MPA, GPA, and EGPA), the frequency of rs1128334A was compared between patients of each AAV subset and healthy controls. No deviation of genotype distribution from Hardy–Weinberg equilibrium was observed in healthy controls (Hardy–Weinberg equilibrium test, $P = 0.27$). As shown in Table 2, rs1128334A was significantly increased in GPA compared with healthy controls under the additive

model for the A allele ($P = 0.0060$, $P_c = 0.030$; odds ratio (OR), 1.54; 95% confidence interval (CI), 1.13–2.10). No significant association was detected in MPA or EGPA (Table 2).

Next, the association of rs1128334 genotype with ANCA specificity of the AAV patients was examined. Significant increase of rs1128334A was observed in PR3–AAV ($P = 0.0042$, $P_c = 0.021$; OR, 1.72; 95% CI, 1.19–2.49). The same trend for association was also observed in MPO–AAV, although the difference did not reach statistical significance after Bonferroni correction ($P = 0.032$, $P_c = 0.16$; OR, 1.20; 95% CI, 1.02–1.43).

Statistical significance in association with GPA and PR3–AAV remained after adjustment for the gender difference between the patients and controls (GPA: $P_{adjusted} = 0.0082$; OR, 1.52; 95% CI, 1.11–2.07; PR3–AAV: $P_{adjusted} = 0.0068$; OR, 1.67; 95% CI, 1.15–2.43).

In the European and North American populations, *HLA-DPB1*04:01* was associated with susceptibility to GPA [5, 8]. We also reported a trend for association of *HLA-DPB1*04:01* with PR3–AAV in a Japanese population [4]. Therefore, we examined genetic interaction between *ETS1* and *HLA-DPB1*04:01*. No evidence for genetic interaction between *ETS1* rs1128334 and *HLA-DPB1*04:01* was observed in the analysis of GPA or PR3–AAV (GPA: $P = 0.75$, PR3–AAV: $P = 0.66$).

Discussion

In this study, we detected association of a SNP rs1128334, located in the 3′UTR of *ETS1*, with GPA and PR3–AAV in a Japanese population. The risk allele, rs1128334A, was the same as in SLE and AS [25, 27]. Because of the low incidence of GPA and PR3–AAV in the Japanese population [2], the sample size of these subsets was small; nevertheless, the association remained significant after Bonferroni correction. Furthermore, although statistically not significant after Bonferroni correction, MPO–AAV also showed a similar trend for association. Although the sample size was larger than in GPA and PR3–AAV, the detection power was still not sufficient for MPA and MPO–AAV (0.445 and 0.565, respectively); therefore, these results need to be confirmed in future studies with a larger sample size.

To our knowledge, this is the first report to suggest association of *ETS1* SNPs with AAV. A previous study in European populations reported that rs6590330, located downstream of *ETS1* and is in almost absolute LD with rs1128334, did not detect any trend toward association with GPA (rs6590330A: OR, 0.98; $P = 0.800$) [30]. In SLE, the association of rs1128334 or rs6590330 was not detected in European GWAS; however, suggestive association with rs6590330 in European populations was detected when it was examined as a candidate SNP [26]. Frequency of the risk allele, rs1128334A, appears to be higher in Asian populations (0.351 in Hong Kong Chinese [25] and 0.387 in Japanese) as compared with that in European populations (0.106 in the HapMap CEU (residents with Northern and Western European ancestry from the CEPH collection)). Thus, it is possible that the genetic association was more sensitively detectable in the Asian populations.

rs1128334A, located in the 3′UTR of *ETS1*, was previously associated with reduced expression of *ETS1* [25], and was predicted to constitute a binding site of microRNA, miR-381 in TargetScan Release 7.1 (http://www.targetscan.org/vert_71/). It was also reported that the SLE risk allele in rs6590330 was associated with increased binding of phosphorylated STAT1 (pSTAT1) to putative STAT1-binding site near rs6590330 and with decreased *ETS1* expression [31]. These studies suggest the functional significance of both rs1128334 and rs6590330. In addition, the possibility that polymorphisms other than rs6590330 that are in LD with rs1128334 may have a functional role cannot be ruled out at this point. Twenty-one polymorphisms including rs6590330 show LD ($r^2 \geq 0.6$) with rs1128334.

ETS1 has been shown to inhibit differentiation of plasma cells and Th17 cells, and to induce development of Tregs [23]. Th17 cells were reported to be increased in GPA patients [32]. Furthermore, when peripheral blood cells from the GPA patients were stimulated with PR3 in vitro, Th17 cells have been shown to increase in PR3–ANCA positive, but not in PR3–ANCA negative, GPA patients [33], suggesting that Th17 cells play a role in the pathogenesis of GPA. Moreover, functionally Ets1-deficient mice lacking the pointed domain of *Ets1* showed increased plasma cell differentiation and production of autoantibodies upon TLR9 stimulation [34]. Taken together with these functional studies, our findings suggest that genetically determined reduced expression of ETS1 may result in T-cell and B-cell abnormalities, which eventually play a role in AAV.

Limitations of this study include small sample size of GPA and PR3–AAV, due to the low prevalence of these subsets in Japan. The annual incidence of GPA has been reported to be 2.1/million in Japan [2], and the total number of the registered patients of GPA in the year of 2015 in Japan was 2534, according to the report from Japan Intractable Diseases Information Center (http://www.nanbyou.or.jp/entry/5354). In fact, our current sample size was accomplished by nearly 20 years of nationwide collaboration, and is one of the largest among AAV genetics studies in Asian populations. Nevertheless, the association detected in this study needs to be replicated in future independent studies. Further extension of collaboration network is currently underway.

Case–control association studies suffer from the population stratification issue. It is generally considered that this

may not be a critical problem in the Japanese population. Yamaguchi-Kabata et al. performed a principal component analysis based on 140,387 SNPs in 7003 Japanese individuals, and demonstrated that Japanese individuals were divided into two clusters, Hondo and Ryukyu, the latter includes most of the individuals from Okinawa (94.7%), and suggested that the differences in the proportion of the individuals from the Ryukyu cluster may affect the results of the case–control study [35]. However, the proportion of the individuals with the Ryukyu cluster is <3% in all regions of mainland islands of Japan, except for the Kyushu region (10.47%).

In our study, none of the controls were recruited in Okinawa and Kyushu regions, and among the patients with GPA and/or PR3–ANCA positive AAV, only two were recruited in Kyushu. Exclusion of these patients from analysis did not alter the association results (GPA vs. controls: uncorrected $P = 0.0047$, PR3–ANCA positive AAV vs. controls: uncorrected $P = 0.0045$). Thus, we believe that population stratification was not a major problem in this study.

In conclusion, this study suggested that a SNP associated with low expression of *ETS1* is associated with susceptibility to GPA and PR3–AAV in a Japanese population. Although future replication studies are necessary, *ETS1* was suggested to be a genetic factor shared by multiple autoimmune diseases in Asian populations.

Acknowledgments The authors are grateful to the patients and healthy donors who participated in this study, and to the doctors who recruited patients to the projects of the Research Committee on intractable vasculitides and the Japanese RPGN Study Group of progressive renal disease, Ministry of Health, Labor and Welfare of Japan (including remission induction therapy in Japanese patients with ANCA-associated vasculitides (RemIT-JAV), remission induction therapy in Japanese patients with ANCA-associated vasculitides and rapidly progressive glomerulonephritis (RemIT-JAV-RPGN), and Japanese patients with MPO ANCA-associated vasculitis (JMAAV)) and directly to this study. This work was supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI (Grant numbers 25461467 and 16K09886), Japan Agency for Medical Research and Development (AMED) "The Strategic Study Group to Establish the Evidence for Intractable Vasculitis Guideline (Grant numbers 16ek0109121h0002 and 17ek0109121s0403)" and "The Study Group for Strategic Exploration of Drug Seeds for ANCA-Associated Vasculitis and Construction of Clinical Evidence (Grant number 16ek0109104h0002 and 17ek0109104s0203)", the Japan Rheumatism Foundation, the Japan College of Rheumatology, and the SENSHIN Medical Research Foundation.

Compliance with ethical standards

Conflict of interest FH is employed by the Department of Lifetime Clinical Immunology, Tokyo Medical and Dental University (TMDU), which has received unrestricted research grants from Chugai Pharmaceutical Co., Ltd., Ono Pharmaceuticals, Mitsubishi Tanabe Pharma Co., UCB Japan, CSL Behring, Towa Pharmaceutical Co., Ltd., Abbvie Japan Co., Ltd., Japan Blood Products Organization, Ayumi Pharmaceutical Co., and Nippon Kayaku Co., Ltd. TS received honoraria for lectures from Mitsubishi Tanabe Pharma Co., Ltd., and research grants from Mitsubishi Tanabe Pharma Co., Ltd., Chugai Pharmaceutical Co., Ltd., Astellas Pharma Co., Ltd., and Ono Pharmaceutical Co., Ltd. ST received honoraria for lectures from Pfizer, and a research grant from Chugai Pharmaceutical Co., Ltd. HM serves as a consultant for Abbvie Japan Co., Ltd. and Teijin Pharma Ltd. MH has received a research grant from Abbvie. Tokyo Women's Medical University (TWMU), particularly the Division of Epidemiology and Pharmacoepidemiology in Rheumatic Diseases, has received unrestricted research grants from Ayumi Pharmaceutical Co., Chugai Pharmaceutical Co., Ltd., Eisai Co., Ltd., Nippon Kayaku Co., Ltd., Taisho Toyama Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Co., and Teijin Pharma Ltd., with which TWMU paid the salary of MH. NT received 2017 Novartis—Japan Rheumatism Foundation Rheumatology Prize. The remaining authors declare no conflict of interest.

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