Table 2. Distribution and correlates of ACPA and RF in the general population*

		ACPA			RF		
	No.	Positivity, %	*P*†	OR (95% CI)†	Positivity, %	*P*†	OR (95% CI)†
All subjects	9,575	1.7	–	–	6.4	–	–
Sex							
Male	3,168	1.7	–	Reference	5.7	–	Reference
Female	6,407	1.8	0.84	1.04 (0.74–1.45)	6.8	0.040	1.21 (1.00–1.45)
Age, years							
30–39	2,315	1.3	–	Reference	5.4	–	Reference
40–49	1,339	1.3	0.94	0.98 (0.53–1.80)	5.8	0.67	1.06 (0.79–1.44)
50–59	1,886	1.8	0.23	1.35 (0.82–2.25)	8.7	5.4×10^{-5}	1.64 (1.29–2.10)‡
60–69	3,012	1.8	0.12	1.43 (0.90–2.26)	6.3	0.13	1.20 (0.95–1.52)
70–75	1,023	3.0	0.00062	2.46 (1.45–4.15)‡	5.7	0.67	1.07 (0.77–1.49)
BMI, kg/m^2							
18.5–25	6,876	1.8	–	Reference	6.6	–	Reference
<18.5	902	1.2	0.37	0.75 (0.39–1.42)	6.7	0.88	1.02 (0.76–1.37)
25–30	1,567	2.0	0.71	1.08 (0.72–1.63)	5.5	0.15	0.84 (0.66–1.07)
≥30	230	1.3	0.66	0.77 (0.24–2.51)	7.0	0.72	1.10 (0.65–1.86)
Smoking							
Never	6,219	1.7	–	Reference	6.7	–	Reference
Ex-smoker	1,961	2.0	0.21	1.36 (0.83–2.20)	5.8	0.97	1.00 (0.77–1.31)
Active	1,395	1.6	0.49	1.22 (0.69–2.16)	6.2	0.46	1.11 (0.83–1.49)
0 < BI ≤ 200	1,056	1.5	0.65	1.14 (0.65–2.02)	5.0	0.23	0.83 (0.61–1.13)
200 < BI ≤ 600	1,254	1.7	0.32	1.34 (0.75–2.39)‡	5.3	0.82	1.04 (0.75–1.43)
600 < BI	1,044	2.2	0.32	1.42 (0.71–2.83)‡	7.5	0.018	1.58 (1.08–2.30)‡
Alcohol§							
Never or past	3,193	2.1	–	Reference	6.3	–	Reference
Current, light	1,883	1.8	0.66	0.91 (0.58–1.41)	7.3	0.049	1.26 (1.00–1.60)
Current, moderate/heavy	3,396	1.3	0.025	0.60 (0.38–0.95)§	5.8	0.84	1.02 (0.81–1.29)
CRP, mg/dl							
<0.1	1,587	1.1	–	Reference	5.4	–	Reference
0.1–0.3	3,350	1.7	0.27	1.36 (0.78–2.37)	6.4	0.17	1.20 (0.92–1.58)
>0.3–1.0	3,235	1.5	0.64	1.14 (0.64–2.06)	6.4	0.30	1.16 (0.87–1.53)
≥1.0	1,403	3.0	0.0078	2.26 (1.22–4.17)‡	7.5	0.0087	1.53 (1.11–2.12)‡

* ACPA = anti–citrullinated peptide antibody; RF = rheumatoid factor; OR = odds ratio; 95% CI = 95% confidence interval; BMI = body mass index; BI = Brinkman's Index; CRP = C-reactive protein.
† Logistic regression analysis adjusting for sex and age (statistics for BMI, alcohol, smoking, and CRP level).
‡ Suggestive or significant associations mentioned in the main text.
§ Those that drink more than once a week are categorized as moderate/heavy.

any significant associations for BMI, smoking, and alcohol consumption (Table 2), high alcohol consumption showed a suggestive protective effect with ACPA positivity, consistent with the previous report from European populations showing a protective effect of alcohol consumption against ACPA-positive RA (34). Smoking showed a suggestive dose-dependent effect on ACPA production, and this effect was strengthened in condition with alcohol consumption (Table 2 and Supplementary Table 4, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22385/abstract). A high level of CRP showed suggestive associations with ACPA and RF positivity (P = 0.0078 and 0.0087, respectively) (Table 2). Because smoking is the established environmental risk factor for seropositive RA, especially in men, we separately analyzed effects of smoking on ACPA and RF production in men and women. As a result, while we found a slight increase of positivity in male ever-smokers, the associations did not reach a significant level and the ORs were much lower than those for seropositive RA (Table 3).

The linear increase of ACPA positivity according to ages of individuals raised the possibility that the positive likelihood ratio (PLR) of having RA based on ACPA positivity differed according to the age groups. To address this point, we collected ACPA data from 2,067 patients with RA whose data on age at onset were available and calculated the PLR of having RA based on ACPA positivity. As a result, we found that the PLR of having RA decreased according to age (Supplementary Figure 2A, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22385/abstract). In particular, the group age >70 years demonstrated a significantly lower PLR of RA than the group ages 30–39 years (P = 0.0033) (Supplementary Figure 2A, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/ acr.22385/abstract). When we analyzed RF positivity in the same manner, the PLR decreased in the group ages 50–59 years in comparison to the group ages 30–39 years, reflecting an increase of RF positivity in the general population (P = 0.0013) (Supplementary Figure 2B, available in the online version of this article

Table 3. Lack of significant association between smoking and ACPA or RF in men and women*

All subjects	ACPA				RF			
	No.	Positivity, %	P†	OR (95% CI)†	No.	Positivity, %	P†	OR (95% CI)†
Men								
Never	791	1.3	–	Reference	791	4.7	–	
Ex-smoker	1,399	2.1	0.25	1.62 (0.71–3.66)	1,399	5.8	0.55	Reference
Active	978	1.5	0.38	1.50 (0.60–3.74)	978	6.3	0.13	1.14 (0.74–1.76)
Ever (Ex and Active)	2,377	1.9	0.27	1.54 (0.71–3.36)	2,377	6.0	0.28	1.42 (0.91–2.23)
0 < BI ≤ 200	436	1.6	0.67	1.31 (0.38–4.49)	436	5.0	0.72	1.24 (0.84–1.84)
200 < BI ≤ 600	943	1.5	0.53	1.35 (0.53–3.45)	943	4.8	0.99	1.11 (0.62–2.00)
600 < BI	981	2.3	0.27	1.60 (0.70–3.69)	981	7.6	0.10	1.00 (0.62–1.62)
Women								1.46 (0.93–2.29)
Never	5,428	1.8	–	Reference	5,428	6.9	–	
Ex-smoker	562	1.8	0.60	1.22 (0.59–2.50)	562	5.7	0.30	Reference
Active	417	1.7	0.51	1.31 (0.59–2.91)	417	6.0	0.53	0.80 (0.52–1.22)
Ever (Ex and Active)	979	1.7	0.44	1.25 (0.71–2.21)	979	5.8	0.27	0.86 (0.53–1.38)
0 < BI ≤ 200	620	1.5	0.73	1.13 (0.55–2.35)	620	5.0	0.063	0.83 (0.59–1.15)
200 < BI ≤ 600	311	2.3	0.20	1.68 (0.76–3.72)	311	7.1	0.55	0.65 (0.42–1.02)
600 < BI	41	0	0.98	NA	41	7.3	0.73	1.15 (0.72–1.84)

* ACPA = anti–citrullinated peptide antibody; RF = rheumatoid factor; OR = odds ratio; 95% CI = 95% confidence interval; BI = Brinkman's Index; NA = not applicable.
† *P* values and ORs in logistic regression analysis using age and alcohol drinking as covariates.

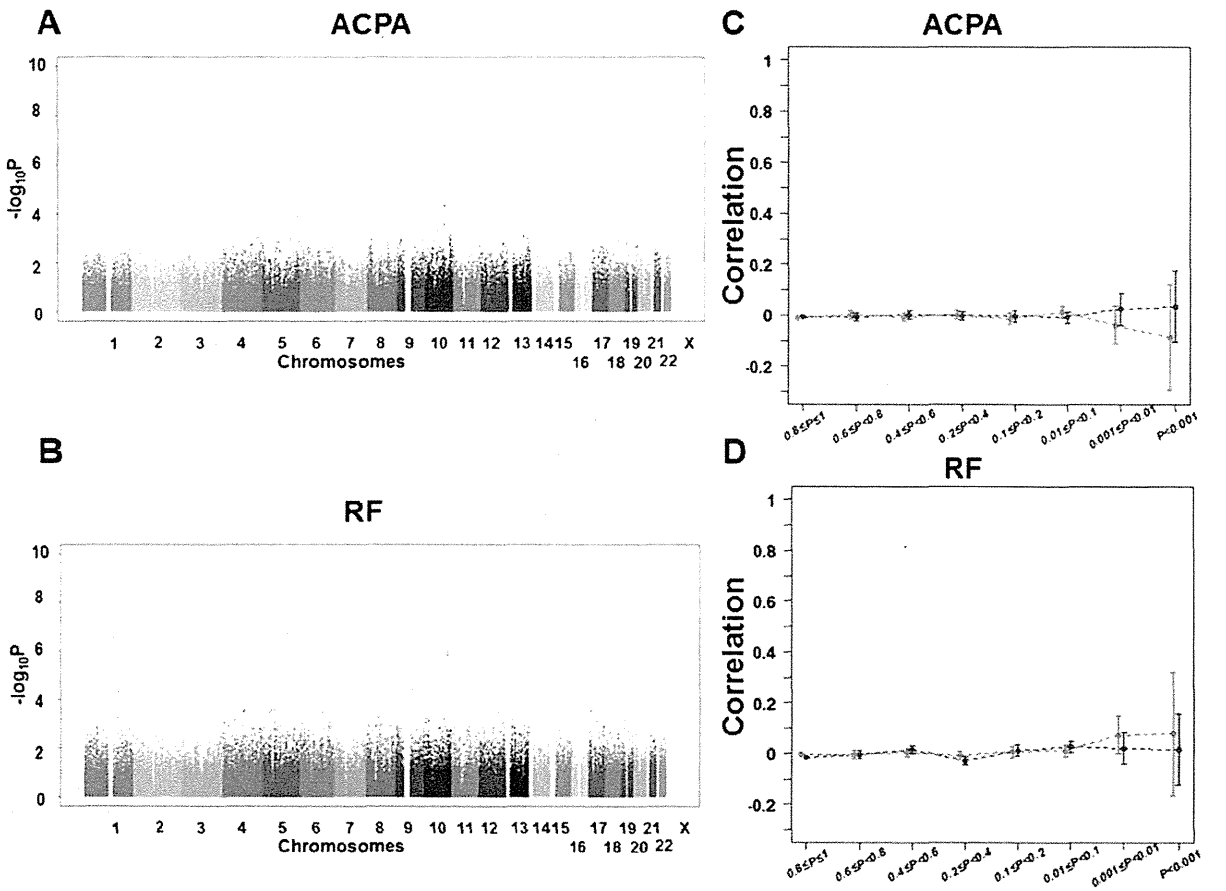

Figure 1. Genetic associations of single-nucleotide polymorphism (SNPs) and anti–citrullinated peptide antibody (ACPA) or rheumatoid factor (RF) positivity. Manhattan plot is shown for positivity of ACPA (**A**) or RF (**B**). No SNPs showed significant associations with positivity of ACPA or RF. Limited correlations of odds ratios in the SNPs of genome-wide association studies between RA susceptibility and positivity of ACPA (**C**) or RF (**D**). Blue broken lines indicate SNPs with *P* values in the range of x-axis for positivity of ACPA (**C**) or RF (**D**). Red broken lines indicate SNPs with *P* values in the range of x-axis for RA susceptibility. SNPs are pruned by $r^2 < 0.3$. The error bars indicate 95% confidence interval.

Table 4. Lack of significant associations between positivity of ACPA or RF and combination of SE and smoking in the general population*

		ACPA			RF		
	No.	Positivity, %	P†	OR (95% CI)†	Positivity, %	P†	OR (95% CI)†
SE (-)	1,935	1.7	–	Reference	6.0	–	Reference
SE (+)	1,235	1.9	0.82	0.93 (0.47–1.81)	6.8	0.95	1.01 (0.71–1.44)
All subjects							
SE (-) nonsmoker	1,230	1.8	–	Reference	6.4	–	Reference
SE (-) ex-smoker	373	2.4	0.063	2.83 (0.94–8.46)	4.3	0.16	0.58 (0.27–1.24)
SE (-) current smoker	332	0.6	0.40	0.50 (0.10–2.47)	6.0	0.64	0.84 (0.41–1.74)
SE (-) BI	–	–	0.045	1.13 (1.00–1.27)	–	0.24	1.05 (0.97–1.13)
SE (+) nonsmoker	772	2.1	0.50	1.32 (0.59–2.98)	7.0	0.89	0.97 (0.63–1.48)
SE (+) ex-smoker	265	1.9	0.65	1.41 (0.31–6.33)	7.2	0.75	0.88 (0.41–1.89)
SE (+) current smoker	198	1.0	0.68	0.71 (0.14–3.63)	5.6	0.44	0.68 (0.25–1.82)
SE (+) BI	–	–	0.26	0.84 (0.62–1.14)	–	0.48	0.96 (0.86–1.07)
Male							
SE (-) smoking (-)	184	1.1	–	Reference	6.0	–	Reference
SE (-) smoking (+)	461	1.5	0.65	1.45 (0.30–7.07)	5.2	0.51	0.75 (0.33–1.75)
SE (-) BI	–	–	0.38	1.06 (0.93–1.20)	–	0.24	1.05 (0.97–1.14)
SE (+) smoking (-)	93	3.2	0.25	2.97 (0.48–18.44)	2.2	0.20	0.36 (0.08–1.73)
SE (+) smoking (+)	334	1.8	0.53	1.69 (0.33–8.52)	6.0	0.51	0.74 (0.31–1.81)
SE (+) BI	–	–	0.33	0.92 (0.78–1.09)	–	0.23	0.93 (0.83–1.05)
Female							
SE (-) smoking (-)	1,046	1.9	–	Reference	6.6	–	Reference
SE (-) smoking (+)	244	1.6	1.00	1.00 (0.32–3.15)	4.9	0.28	0.61 (0.25–1.50)
SE (-) BI	–	–	–	–	–	0.93	1.01 (0.80–1.27)
SE (+) smoking (-)	679	1.9	0.81	1.10 (0.53–2.26)	7.7	0.84	1.05 (0.65–1.69)
SE (+) smoking (+)	129	0.8	0.44	0.44 (0.06–3.43)	7.8	0.81	0.88 (0.30–2.61)
SE (+) BI	–	–	–	–	–	0.24	1.18 (0.90–1.56)

* ACPA = anti–citrullinated peptide antibody; RF = rheumatoid factor; SE = shared epitope; OR = odds ratio; 95% CI = 95% confidence interval; BI = Brinkman's Index.
† Logistic regression analysis adjusting for age, sex, and alcohol consumption or age and alcohol consumption for the analysis of all subjects and men or women, respectively. Results of logistic regression analysis adjusting for only age were shown for ACPA analyses of men, women, and subgroup with <5 subjects positive for ACPA. Linear regression analysis of BI was applied for subsets with >5 smoking subjects.

at http://onlinelibrary.wiley.com/doi/10.1002/acr.22385/abstract).

Genetic components. Next we performed a GWAS in 3,170 healthy subjects to estimate common variants associated with positivity of ACPA or RF. The GWAS did not show population stratification in both studies ($\lambda \leq 1.00$). Both GWAS did not demonstrate significant associations ($P < 5 \times 10^{-8}$) in any markers, including the HLA locus (Figures 1A and B). Due to limitations of sample sizes with positive ACPA or RF in the current study and the possibility of multiple variants with low effect sizes associated with the phenotypes, it could be that truly associated SNPs were enriched in the SNP group with suggestive associations, even if we did not find markers with significant associations. As previous genetic studies have suggested that SNPs with low to middle effect sizes contribute to RA phenotypes beyond ethnicity (19) even if they did not show significant associations, we hypothesized that multiple common variants with low to middle effect sizes contributing to RA would be associated with ACPA or RF production in the general population and vice versa. Therefore, we performed correlation analyses to compare the effect sizes of SNPs between the RA study and the 2 GWASs. We used data of the RA GWAS that recruited 1,237 cases and 2,087 controls in Kyoto University, which was a part of a previously published meta-analysis in a Japanese population (19). As a result, we did not find significant correlations between RA susceptibility and RF or ACPA positivity, even in a set of SNPs showing P values less than 0.001 in each GWAS ($P \geq 0.40$) (Figure 1C and D).

HLA–DRB1 and positivity of ACPA and RF. Since the association between SE and positivity of ACPA and RF in patients with RA is well established, we analyzed whether these associations were observed in the general population. We imputed HLA–DRB1 alleles in the 3,170 individuals by HLA–IMP2 based on the genome-scanning data (details shown in Patients and Methods). Imputation of SE showed more than 93.5% of sensitivity and 99.8% of specificity for the genotyped SE in the 2 independent sets. The association studies showed that SE was not significantly associated with ACPA and RF positivity ($P = 0.82$ and 0.95, respectively) (Table 4). Because previous studies showed that associations between SE and positivity for ACPA and RF in patients with RA were strengthened in the smoking population, we classified our subjects into 3 groups according to smoking status and assessed effects of

Table 5. Significant associations between high ACPA level and smoking status or smoking quantity*

		RF high			ACPA high		
	No.	Positivity, %	P†	OR (95% CI)†	Positivity, %	P†	OR (95% CI)†
Smoking (-)	6,219	1.2	–	Reference	0.6	–	Reference
Smoking (+)	3,356	1.5	0.57	1.16 (0.70–1.90)	1.0	0.0019	3.01 (1.50–6.03)‡
Smoking BI	–	–	0.0066	1.08 (1.02–1.15)‡	–	0.00011	1.14 (1.07–1.22)‡
SE (-)	1,935	1.3	–	Reference	0.5	–	Reference
SE (+)	1,235	1.0	0.35	0.75 (0.42–1.37)	0.6	0.46	1.33 (0.62–2.84)

* Nonsmoking subjects without rheumatoid factor (RF) or anti–citrullinated peptide antibody (ACPA) were set as reference for the analysis of smoking. Subjects without shared epitope (SE) and RF or ACPA were set as reference for the analysis of SE. OR = odds ratio; 95% CI = 95% confidence interval; BI = Brinkman's Index.
† Logistic regression analysis adjusting for age, sex, and alcohol drinking, or age and sex for the analysis of smoking or SE, respectively.
‡ Suggestive or significant associations mentioned in the main text.

SE. We did not find significant associations in any of the 3 groups (nonsmoking, ex-smoking, and currently smoking) (Table 4) and smoking quantity. As a previous study suggested that male subjects with SE are more sensitive to smoking in ACPA production (35), men and women were analyzed separately. We found an increase of ACPA positivity in SE-positive groups both for male nonsmoking and smoking groups, but the associations did not reach the significant level (Table 4).

Association between high level of ACPA and smoking or SE. Because the distribution of ACPA or RF levels in subjects positive for these antibodies is different between healthy people and patients with RA (see Supplementary Table 5, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22385/abstract), we focused on those individuals with high levels of ACPA or RF. While the decreased number of positive subjects made it difficult to conclude the association, we observed a significant association between smoking and high levels of ACPA with a comparable effect size to patients with RA ($P = 0.0019$, OR 3.01 [95% CI 1.50–6.03]) (Table 5). Further, smoking showed a dose-dependent association with high levels of ACPA ($P = 0.00011$). Although smoking did not show association with high levels of RF, we observed a suggestive dose-dependent effect of smoking on high RF production ($P = 0.0066$) (Table 5). We found that the association trend between smoking and high ACPA levels was enhanced in male subjects (Supplementary Table 6, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22385/abstract). On the contrary, we did not find associations between SE and high levels of RF or ACPA.

DISCUSSION

In the current study, we showed positivity of ACPA and RF in the general population, analyzed correlates of these autoantibodies, and assessed genetic effects alone and in combination with smoking. This is the first study to quantify ACPA and RF in a large-scale healthy population to assess correlates. Although the positivity of ACPA in this study was comparable to that in the previous Turkish study (1.0% in 941 subjects) (36), the positivity of RF was slightly higher than those in the previous study that were highly variable (21,25,36). This high positivity of RF in the current study may be explained by the high proportion of female subjects who showed a suggestive increase of RF positivity compared to men, and the high proportion of subjects in their 50s who showed the highest positivity of RF among the groups. The 201 subjects excluded due to possibly having connective tissue diseases showed positivity of 27.9% and 34.8% for ACPA and RF, respectively, reflecting that many of them have rheumatic diseases (data not shown). Considering the prevalence of RA patients in the Japanese population (0.5–1.0%), the frequency of excluded subjects in the current study (approximately 2% of study subjects) seems reasonable. Therefore, it is less likely that patients with RA were missed for exclusion and enriched in the remaining subjects. The cutoff values of 26 and 45 IU/ml for RF would give 95% and 98% specificity in the current study, respectively. ACPA showed more than 98% specificity with the current cutoff value.

The positivity of ACPA and RF showed correlations even in the general population. Although the OR of being positive for both autoantibodies is lower than that in patients with RA (the 2,067 patients in this study: OR 24.79 [95% CI 17.84–34.45]; data not shown), the titers in subjects positive for both autoantibodies also showed a good correlation. These might suggest that both autoantibodies share common genetic and/or environmental risk factors.

ACPA and RF positivity did not show strong association with sex. As approximately 80% of RA patients are women (37), the lack of association suggests that factors other than sex are essential to produce ACPA and RF. We detected an age-dependent increase of ACPA positivity. This result corresponds to a previous report suggesting that detectable levels of antibodies against fillagrin, one of the important targets of citrullination of RA, tended to be found in the older population (38). RF showed an inverse U pattern in association with age. Menopausal term seems to correspond to the peak of RF positivity in female subjects. However, when we divided female subjects ages 50–59 years into 2 groups based on menopause, we did not find a significant difference in the positivity of RF ($P = 0.31$ and OR 0.78; data not shown). The same tendency of

increase of RF positivity in men cannot be explained by menopause. A prospective study to follow the same participants to observe the level of RF and compare RF positivity before and after menopause may lead to more clues for mechanisms underlying RF production. Previous studies showed that the elderly population has high frequency of RF in Europe and the US (24,25). Men showed the suggestive association between aging and RF production in this study. The difference between populations may suggest that different environmental factors play a role in autoantibody production. In fact, a recent twin study analyzing ACPA revealed that large parts of variance of ACPA can be explained by nonshared environmental factors (39). Different PLRs suggest that when individuals were incidentally found to be positive for these autoantibodies, ACPA in particular, the likelihood of having RA or having risk of RA is different based on age.

Analysis of candidates of correlates for ACPA and RF resulted in a positive association between high levels of CRP and ACPA or RF positivity. While this suggests an association between the production of these autoantibodies with preclinical inflammation, the current cross-sectional study could not conclude whether the production is a cause or a result. Other candidates for correlates were not associated with ACPA or RF. Many studies recruiting RA patients have shown that smoking is a strong environmental factor to produce ACPA and to develop RA (17,35). In our study, the associations between smoking and ACPA or RF positivity are not significant, while we observed significant or suggestive dose-dependent effects of smoking on high levels of ACPA or RF, respectively. A previous European study showed an association between active smoker and RF production in a healthy population (23). Since the median BI was 370 in the ever-smokers in the current study, equivalent to 1 pack a day for approximately 18 years, the less amount of smoking may contribute to a low effect of smoking status on autoantibody production in the current study. Previous studies revealed that ever smoking showed an OR of approximately 3 for male seropositive RA and 1.3 for female (18). Based on the seropositivity of nonsmokers, the current study is powered 100% in men and 68% in women to detect the effects with an OR of 3 and 1.3, respectively, at a level of $P = 0.05$. These results suggest that smoking is not associated with production of RF and ACPA at low levels but may be associated with the production of these antibodies at high levels in a healthy population. Although the current study cannot conclude that the association between smoking and high ACPA or RF is true due to the limited number of positive subjects, it is feasible to increase the number of healthy subjects. It will also be interesting to analyze smoking effects on low ACPA or RF levels in patients with RA. Isotypes of RF and ACPA were not quantified in the current study. Detailed classification of RF and ACPA would reveal specific associations of correlates, especially smoking.

While a recent twin study showed that heritability of ACPA was 0.23 (39), GWAS for positivity of RF or ACPA resulted in no significant signals, including the HLA locus. Our study had a power of 0.99 to detect an SNP with allele frequency of 0.4 (SE-positive ratio in healthy subjects) and an OR of 2.0 associated with 7% of frequent phenotype at a level of $P = 0.00001$. Our study also had a power of 0.42 to detect an SNP associated with 1.6% frequent phenotype at a level of $P = 0.01$. The imputed SE showed an OR of 1.15 for both ACPA and RF. Considering an OR of 2.0–3.0 in patients with RA for positivity of RF or ACPA in the previous studies, the current study indicates that SE was not similarly associated with ACPA and RF production in the general population as in RA patients. Furthermore, we did not observe associations between SE and high ACPA or RF. ACPA and RF production may need other factors than SE, such as chronic inflammatory stimulation. While the male population showed suggestive associations between SE and ACPA production, the limited number of the positive subjects did not allow us to draw any conclusions. Common direction of SE and smoking for ACPA production in men suggests that men are more sensitive to these risk factors than women. Although previous studies reported that HLA–DRB1*09:01 had a lowering effect of ACPA in the Japanese (27), we did not find a significant effect of *09:01 on ACPA positivity (Supplementary Table 7, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22385/abstract). HLA–DR13, especially DRB1*13:01, shows a negative association with ACPA-positive RA in the European population (40). Although we did not find ACPA-positive subjects with DRB1*13:01 in the current study (Supplementary Table 7, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22385/abstract), low frequency of DRB1*13:01 made it difficult to conclude the association between ACPA production and DRB1*13:01. No associations were detected between DR13 and ACPA production either. The negative results of genetic correlation analyses suggest that RA susceptibility and ACPA or RF production in the general population share limited genetic components in spite of wide confidence intervals of SNPs due to low power of the current study.

Because disease-specific autoantibodies, including ACPA and RF, were shown to appear several years before the diagnosis of the diseases (21,41–45), it will be interesting to follow the current study population to observe whether or not they will develop RA. It will also be very interesting to validate our results in other populations and compare the associations among the different populations.

ACKNOWLEDGMENTS

The authors are grateful to the Nagahama City Office and the nonprofit organization Zeroji Club for their help in performing the Nagahama Study.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Terao had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Terao, Ohmura, Ikari, Kawaguchi, Takahashi, Setoh, Nakayama, Kosugi, Sekine, Tabara, Taniguchi, Momohara, Yamanaka, Yamada, Matsuda, Mimori.

Acquisition of data. Terao, Ohmura, Ikari, Kawaguchi, Takahashi, Setoh, Nakayama, Kosugi, Sekine, Tabara, Taniguchi, Momohara, Yamanaka, Yamada, Matsuda, Mimori.
Analysis and interpretation of data. Terao, Kawaguchi.

REFERENCES

1. Nishimura K, Sugiyama D, Kogata Y, Tsuji G, Nakazawa T, Kawano S, et al. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. Ann Intern Med 2007;146:797–808.
2. Renaudineau Y, Jamin C, Saraux A, Youinou P. Rheumatoid factor on a daily basis. Autoimmunity 2005;38:11–6.
3. Shmerling RH, Delbanco TL. The rheumatoid factor: an analysis of clinical utility. Am J Med 1991;91:528–34.
4. Clifford BD, Donahue D, Smith L, Cable E, Luttig B, Manns M, et al. High prevalence of serological markers of autoimmunity in patients with chronic hepatitis C. Hepatology 1995;21: 613–9.
5. Pawlotsky JM, Roudot-Thoraval F, Simmonds P, Mellor J, Ben Yahia MB, Andre C, et al. Extrahepatic immunologic manifestations in chronic hepatitis C and hepatitis C virus serotypes. Ann Intern Med 1995;122:169–73.
6. Yoshida H, Imafuku Y, Morita EO, Nagai T, Kato Y, Motegi S. Detection of antinuclear antibodies and their significance as disease markers. Rinsho Byori 1994;42:455–9. In Japanese.
7. Tan EM, Feltkamp TE, Smolen JS, Butcher B, Dawkins R, Fritzler MJ, et al. Range of antinuclear antibodies in "healthy" individuals. Arthritis Rheum 1997;40:1601–11.
8. Cammarata RJ, Rodnan GP, Fennell RH. Serum anti-gammaglobulin and antinuclear factors in the aged. JAMA 1967;199: 455–8.
9. Fairweather D, Frisancho-Kiss S, Rose NR. Sex differences in autoimmune disease from a pathological perspective. Am J Pathol 2008;173:600–9.
10. Schellekens GA, Visser H, de Jong BA, van den Hoogen FH, Hazes JM, Breedveld FC, et al. The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. Arthritis Rheum 2000;43:155–63.
11. Kuhn KA, Kulik L, Tomooka B, Braschler KJ, Arend WP, Robinson WH, et al. Antibodies against citrullinated proteins enhance tissue injury in experimental autoimmune arthritis. J Clin Invest 2006;116:961–73.
12. Vittecoq O, Pouplin S, Krzanowska K, Jouen-Beades F, Menard JF, Gayet A, et al. Rheumatoid factor is the strongest predictor of radiological progression of rheumatoid arthritis in a three-year prospective study in community-recruited patients. Rheumatology (Oxford) 2003;42:939–46.
13. De Rycke L, Peene I, Hoffman IE, Kruithof E, Union A, Meheus L, et al. Rheumatoid factor and anticitrullinated protein antibodies in rheumatoid arthritis: diagnostic value, associations with radiological progression rate, and extra-articular manifestations. Ann Rheum Dis 2004;63:1587–93.
14. Vallbracht I, Rieber J, Oppermann M, Forger F, Siebert U, Helmke K. Diagnostic and clinical value of anti-cyclic citrullinated peptide antibodies compared with rheumatoid factor isotypes in rheumatoid arthritis. Ann Rheum Dis 2004;63: 1079–84.
15. Ohmura K, Terao C, Maruya E, Katayama M, Matoba K, Shimada K, et al. Anti-citrullinated peptide antibody-negative RA is a genetically distinct subset: a definitive study using only bone-erosive ACPA-negative rheumatoid arthritis. Rheumatology (Oxford) 2010;49:2298–304.
16. Mattey DL, Dawes PT, Clarke S, Fisher J, Brownfield A, Thomson W, et al. Relationship among the HLA-DRB1 shared epitope, smoking, and rheumatoid factor production in rheumatoid arthritis. Arthritis Rheum 2002;47:403–7.
17. Morgan AW, Thomson W, Martin SG, Yorkshire Early Arthritis Register Consortium, Carter AM, UK Rheumatoid Arthritis Genetics Consortium, et al. Reevaluation of the interaction between HLA-DRB1 shared epitope alleles, PTPN22, and smoking in determining susceptibility to autoantibody-positive and autoantibody-negative rheumatoid arthritis in a large UK Caucasian population. Arthritis Rheum 2009;60: 2565–76.
18. Sugiyama D, Nishimura K, Tamaki K, Tsuji G, Nakazawa T, Morinobu A, et al. Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis 2010;69:70–81.
19. Okada Y, Terao C, Ikari K, Kochi Y, Ohmura K, Suzuki A, et al. Meta-analysis identifies nine new loci associated with rheumatoid arthritis in the Japanese population. Nat Genet 2012;44:511–6.
20. Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis: an approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. Arthritis Rheum 1987;30:1205–13.
21. Nielsen SF, Bojesen SE, Schnohr P, Nordestgaard BG. Elevated rheumatoid factor and long term risk of rheumatoid arthritis: a prospective cohort study. BMJ 2012;345:e5244.
22. Van Schaardenburg D, Lagaay AM, Otten HG, Breedveld FC. The relation between class-specific serum rheumatoid factors and age in the general population. Br J Rheumatol 1993;32: 546–9.
23. Jonsson T, Thorsteinsson J, Valdimarsson H. Does smoking stimulate rheumatoid factor production in non-rheumatic individuals? APMIS 1998;106:970–4.
24. Dequeker J, van Noyen R, Vandepitte J. Age-related rheumatoid factors: incidence and characteristics. Ann Rheum Dis 1969;28:431–6.
25. Waller M, Toone EC, Vaughan E. Study of rheumatoid factor in a normal population. Arthritis Rheum 1964;7:513–20.
26. Yoshimura K, Nakayama T, Sekine A, Matsuda F, Kosugi S, Sugino Y, et al. Prevalence of postmicturition urinary incontinence in Japanese men: comparison with other types of incontinence. Int J Urol 2013;20:911–6.
27. Terao C, Ikari K, Ohmura K, Suzuki T, Iwamoto T, Takasugi K, et al. Quantitative effect of HLA-DRB1 alleles to ACPA levels in Japanese rheumatoid arthritis: no strong genetic impact of shared epitope to ACPA levels after stratification of HLA-DRB1*09:01. Ann Rheum Dis 2012;71:1095–7.
28. Terao C, Ohmura K, Kochi Y, Ikari K, Maruya E, Katayama M, et al. A large-scale association study identified multiple HLA-DRB1 alleles associated with ACPA-negative rheumatoid arthritis in Japanese subjects. Ann Rheum Dis 2011;70:2134–9.
29. Terao C, Ohmura K, Ikari K, Kochi Y, Maruya E, Katayama M, et al. ACPA-negative RA consists of two genetically distinct subsets based on RF positivity in Japanese. PLoS One 2012; 7:e40067.
30. Satoh M, Chan EK, Ho LA, Rose KM, Parks CG, Cohn RD, et al. Prevalence and sociodemographic correlates of antinuclear antibodies in the United States. Arthritis Rheum 2012;64: 2319–27.
31. Dilthey A, Leslie S, Moutsianas L, Shen J, Cox C, Nelson MR, et al. Multi-population classical HLA type imputation. PLoS Comput Biol 2013;9:e1002877.
32. Terao C, Yamada R, Ohmura K, Takahashi M, Kawaguchi T, Kochi Y, et al. The human AIRE gene at chromosome 21q22 is a genetic determinant for the predisposition to rheumatoid arthritis in Japanese population. Hum Mol Genet 2011;20: 2680–5.
33. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet 2007;81:559–75.
34. Pedersen M, Jacobsen S, Klarlund M, Pedersen BV, Wiik A, Wohlfahrt J, et al. Environmental risk factors differ between rheumatoid arthritis with and without auto-antibodies against cyclic citrullinated peptides. Arthritis Res Ther 2006;8:R133.
35. Klareskog L, Stolt P, Lundberg K, Kallberg H, Bengtsson C, Grunewald J, et al. A new model for an etiology of rheumatoid arthritis: smoking may trigger HLA-DR (shared epitope)-restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum 2006;54:38–46.
36. Tasliyurt T, Kisacik B, Kaya SU, Yildirim B, Pehlivan Y, Kutluturk F, et al. The frequency of antibodies against cyclic citrullinated peptides and rheumatoid factor in healthy

population: a field study of rheumatoid arthritis from northern Turkey. Rheumatol Int 2013;33:939–42.
37. Dugowson CE, Koepsell TD, Voigt LF, Bley L, Nelson JL, Daling JR. Rheumatoid arthritis in women: incidence rates in group health cooperative, Seattle, Washington, 1987-1989. Arthritis Rheum 1991;34:1502–7.
38. Palosuo T, Tilvis R, Strandberg T, Aho K. Filaggrin related antibodies among the aged. Ann Rheum Dis 2003;62:261–3.
39. Haj Hensvold A, Magnusson PK, Joshua V, Hansson M, Israelsson L, Ferreira R, et al. Environmental and genetic factors in the development of anticitrullinated protein antibodies (ACPAs) and ACPA-positive rheumatoid arthritis: an epidemiological investigation in twins. Ann Rheum Dis 2013. E-pub ahead of print.
40. Lundstrom E, Kallberg H, Smolnikova M, Ding B, Ronnelid J, Alfredsson L, et al. Opposing effects of HLA-DRB1*13 alleles on the risk of developing anti-citrullinated protein antibody-positive and anti-citrullinated protein antibody-negative rheumatoid arthritis. Arthritis Rheum 2009;60:924–30.
41. Wolfe F, Ross K, Hawley DJ, Roberts FK, Cathey MA. The prognosis of rheumatoid arthritis and undifferentiated polyarthritis syndrome in the clinic: a study of 1141 patients. J Rheumatol 1993;20:2005–9.
42. Rantapaa-Dahlqvist S, de Jong BA, Berglin E, Hallmans G, Wadell G, Stenlund H, et al. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. Arthritis Rheum 2003;48: 2741–9.
43. Arbuckle MR, McClain MT, Rubertone MV, Scofield RH, Dennis GJ, James JA, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. N Engl J Med 2003;349:1526–33.
44. Nielen MM, van Schaardenburg D, Reesink HW, van de Stadt RJ, van der Horst-Bruinsma IE, de Koning MH, et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. Arthritis Rheum 2004;50:380–6.
45. Berglin E, Padyukov L, Sundin U, Hallmans G, Stenlund H, van Venrooij WJ, et al. A combination of autoantibodies to cyclic citrullinated peptide (CCP) and HLA-DRB1 locus antigens is strongly associated with future onset of rheumatoid arthritis. Arthritis Res Ther 2004;6:R303–8.

【VI】班会議プログラム

平成26年度　厚生労働科学研究委託費
難治性疾患等実用化研究事業
免疫アレルギー疾患等実用化研究事業　免疫アレルギー疾患実用化研究分野

関節リウマチの「ドラッグホリデー」と関節破壊「ゼロ」を目指す治療法の確立に関する研究

平成 26 年度　第２回班会議　プログラム・抄録集

・日　時　：　平成２６年１２月１９日（金）１２：３０～１５：００（予定）

・場　所　：　東京ガーデンパレス
（〒113-0034　東京都文京区湯島１－７－５）

平成26年度　厚生労働科学研究委託費
難治性疾患等実用化研究事業
免疫アレルギー疾患等実用化研究事業　免疫アレルギー疾患実用化研究分野

関節リウマチの「ドラッグホリデー」と関節破壊「ゼロ」を目指す治療法の確立に関する研究

◎ Lunch　Time

Ⅰ）開会の辞

１２：５５　～　１３：００

Ⅱ）事務局より

1. 関節リウマチの関節リウマチの「ドラッグホリデー」と関節破壊「ゼロ」を目指す 治療法の確立に関する研究
≪研究代表者≫
産業医科大学医学部　第１内科学講座　教授　田中良哉

１３：００　～　１３：２０

2. FREE-J 経過報告
≪研究協力者≫
産業医科大学医学部 第１内科学講座 平田信太郎

１３：２０　～　１３：４０

Ⅲ）研究班概要発表　（発表時間＋質疑応答＝合計１０分）
3. 関節リウマチ滑膜炎に対する画像検査による観察研究
≪研究分担者≫
北海道大学大学院　医学研究科　免疫・代謝内科学　教授　渥美達也

１３：４０　～　１３：５０

4. 関節エコーを用いた関節リウマチの生物学的製剤(バイオ)フリー寛解維持に関する研究
≪研究分担者≫
長崎大学大学院　医歯学研究科　リウマチ免疫制御学　教授　川上　純

１３：５０　～　１４：００

5. 関節リウマチのリスク遺伝子の病態への寄与に関する研究
≪研究分担者≫
東京医科歯科大学　膠原病・リウマチ内科　教授　上阪　等

１４：００　～　１４：１０

6. MRI 画像による生物学的製剤導入予測基準および中止基準作成に関する研究
≪研究分担者≫
筑波大学大学院　人間総合科学研究科　疾患制御医学専攻　臨床免疫学　教授　住田孝之
１４：１０　～　１４：２０

7. MTX-PG と IL-6 を用いた関節破壊ゼロ予測因子に関する研究
≪研究分担者≫
慶應義塾大学　医学部　リウマチ内科　教授　竹内　勤
（ 発表者 ）
慶應義塾大学　医学部　リウマチ内科　准教授　山岡　邦宏
１４：２０　～　１４：３０

8. 薬剤「フリー」寛解の予測因子としての血中 IL-6 の有用性の検討
≪研究分担者≫
東京医科大学　医学総合研究所　難病分子制御学部門　兼任教授　西本憲弘
１４：３０　～　１４：４０

9. バイオフリー寛解を達成し得た関節リウマチ患者の臨床的・血清学的背景の検討
≪研究分担者≫
京都大学大学院　医学研究科　臨床免疫学　教授　三森経世
１４：４０　～　１４：５０

10. RA 患者末梢血リンパ球における遺伝子発現に注目した寛解の条件とその誘導に関する研究
≪研究分担者≫
東京大学大学院 医学系研究科 内科学専攻 アレルギー・リウマチ学　教授　山本一彦
（ 発表者 ）
東京大学大学院 医学系研究科 内科学専攻 アレルギー・リウマチ学　講師　藤尾圭志

１４：５０　～　１５：００

Ⅲ　開会の辞

１５：００　～