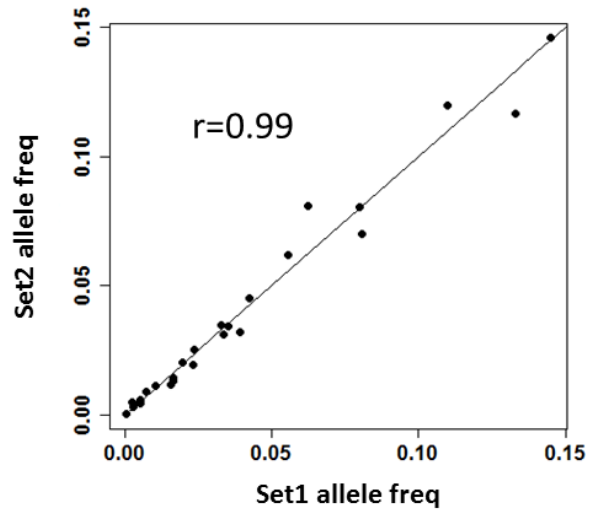Supplementary Materials

Supplementary Figure 1. Strong correlation of allele frequency in control subjects between sets 1 and 2.

Each dot represents each of the all HLA−DRB1 alleles. The diagonal line indicates y=x line.

Supplementary Table 1. Non-additive HLA-DRB1 allelic effects on ACPA(+) RA susceptibility in the common data set.

Allele	Non-additive p	Heterozygote OR (95%CI)	Homozygote OR* (95%CI)
DRB1*01:01	0.27	0.98 (0.85-1.13)	0.82 (0.62-1.09)
DRB1*04:05	8.8×10^{-5}	2.39 (2.12-2.69)	1.85 (1.68-2.03)
DRB1*09:01	0.095	0.87 (0.77-0.98)	0.98 (0.88-1.08)
DRB1*15:01	0.090	0.61 (0.53-0.70)	0.47 (0.36-0.62)
DRB1*15:02	0.00043	0.70 (0.62-0.79)	0.47 (0.38-0.58)

CI: confidence interval

*odds ratio per allele

Supplementary Table 2. Interactive effects of allelic combinations in the common data set.

	DRB1*01:01	DRB1*04:05	DRB1*09:01	DRB1*15:01	DRB1*15:02
DRB1*01:01	–	1.17 (0.81-1.7)	0.81 (0.55-1.21)	2.24 (1.34-3.75)	2.38 (1.55-3.64)
DRB1*04:05	0.4	–	1.15 (0.96-1.38)	1.74 (1.23-2.45)	1.78 (1.36-2.33)
DRB1*09:01	0.3	0.13	–	0.83 (0.56-1.22)	1.09 (0.81-1.46)
DRB1*15:01	2.2×10^{-3}	1.6×10^{-3}	0.34	–	1.06 (0.65-1.73)
DRB1*15:02	6.8×10^{-5}	2.3×10^{-5}	0.58	0.83	–

P-values and OR (95%CI) are indicated in sub- and super-diagnal, respectively. Red colors indicate significant p-values with positive effects.

Supplementary Table 3.   Non-additive effects of amino acid positions on ACPA(+) RA susceptibility.

Position	P	AA	P_AA	allele	AA	P_AA	allele
11	2.2×10^{-4}	V	7.0×10^{-4}	*04:05	S	0.0029	*08:03, *13:02
74	0.0018	A	0.010	*01:01, *04:05, *13:02, *15:01, *15:02			
47	9.5×10^{-5}	Y	9.5×10^{-5}	*01:01, *04:05, *08:03, *09:01			
37	1.6×10^{-5}	Y	3.2×10^{-4}	*04:05, *08:03			

AA: amino acid residues which are the main drivers of associations at the respective positions. HLA-DRB1 alleles included in full data set are indicated.

Supplementary Table 4. Lack of evidence of non-additive HLA-DRB1 effects on ACPA levels in the full data set.

	Non-additive p	Heterozygote Beta (SE)	Homozygote Beta (SE)
DRB1*01:01	0.14	0.13 (0.035)	0.01 (0.076)
DRB1*04:05	0.041	0.15 (0.027)	0.09 (0.022)
DRB1*08:03	0.81	-0.15 (0.043)	-0.13 (0.065)
DRB1*09:01	0.85	-0.25 (0.027)	-0.24 (0.025)
DRB1*13:02	0.26	0 (0.044)	-0.13 (0.101)
DRB1*15:01	0.83	0.17 (0.038)	0.15 (0.081)
DRB1*15:02	0.71	0.15 (0.031)	0.12 (0.063)

SE:standard error

Supplementary Table 5. Lack of evidence of non-additive effects on ACPA levels in the common data set.

Allele	Non-additive p	Heterozygote Beta (SE)	Homozygote Beta (SE)
DRB1*01:01	0.16	0.12 (0.038)	0 (0.077)
DRB1*04:05	0.27	0.11 (0.032)	0.07 (0.023)
DRB1*09:01	0.50	-0.24 (0.031)	-0.26 (0.025)
DRB1*15:01	0.89	0.15 (0.04)	0.14 (0.082)
DRB1*15:02	0.72	0.14 (0.033)	0.11 (0.064)

SE:standard error

Supplementary Table 6. Lack of evidence of interactive effects on ACPA levels in the common data set.

	DRB1*01:01	DRB1*04:05	DRB1*09:01	DRB1*15:01	DRB1*15:02
DRB1*01:01	–	0.104 (0.094)	0.11 (0.103)	0.29 (0.143)	−0.008 (0.116)
DRB1*04:05	0.27	–	0.041 (0.042)	−0.071 (0.095)	0.061 (0.075)
DRB1*09:01	0.29	0.32	–	0.031 (0.115)	0 (0.085)
DRB1*15:01	0.04	0.46	0.79	–	−0.028 (0.145)
DRB1*15:02	0.94	0.42	1	0.85	–

P-values and beta (SE) are indicated in sub- and super-diagonal, respectively.

Supplementary Table 7. Non-additive effects of amino acid positions on ACPA levels

Position	P
74	0.047
57	0.64

Supplementary Table 8. Lack of evidence of interactive effects on ACPA levels in the full data set using ACPA(+) and (−) RA.

	DRB1*01:01	DRB1*04:05	DRB1*08:03	DRB1*09:01	DRB1*13:02	DRB1*15:01	DRB1*15:02
DRB1*01:01	−	0.039 (0.182)	−0.241 (0.243)	0.052 (0.19)	−0.223 (0.299)	0.488 (0.262)	−0.07 (0.207)
DRB1*04:05	0.83	−	−0.318 (0.149)	0.157 (0.068)	0.416 (0.151)	0.49 (0.175)	0.079 (0.126)
DRB1*08:03	0.32	0.03	−	−0.01 (0.138)	0.361 (0.317)	0.403 (0.289)	−0.109 (0.241)
DRB1*09:01	0.78	0.02	0.95	−	0.3 (0.176)	0.454 (0.201)	−0.103 (0.139)
DRB1*13:02	0.46	0.006	0.25	0.09	−	−0.042 (0.341)	−0.51 (0.322)
DRB1*15:01	0.06	0.005	0.16	0.02	0.9	−	0.02 (0.25)
DRB1*15:02	0.73	0.53	0.65	0.46	0.11	0.94	−

P−values and beta (SE) are indicated in sub− and super−diagonal, respectively.