Supplementary Notes

Risk for ACPA-positive rheumatoid arthritis is driven by shared HLA amino acid polymorphisms in Asian and European populations.

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Table S1. Reference panels for HLA variant imputation.

Reference panel	No. subjects	Populations	Cohorts
Pan-Asian panel	530	Asians	Singapore Chinese (*n*=91), Chinese (*n*=111), Indian (*n*=119), Malaysian (*n*=120), HapMap Phase II JPT+CHB (*n*=89)
European panel	120	Europeans	HapMap CEU founders
European panel	5,225	Europeans	T1DGC consortium
Asian & European panel	5,755	Asians & Europeans	Combined panels of Pan-Asians and Europeans (T1DGC)

Table S2. Characteristics of the datasets enrolled in the study.

Population	Study design	Genotyping Platform	No. subjects		References
			RA cases	Controls	
China	GWAS	Affymetrix Genome-wide Human SNP Array 6.0	466	873	Jiang L et al. 2014
South Korea	GWAS	Illumina Human 660W-Quad BeadChip Illumina HumanHap550 BeadChip	799	751	Freudenberg J et al. 2011
South Korea	Immunochip	Illumina Immunochip custom array	1,517	2,691	Kim K et al. 2014
Total	-	-	2,782	4,315	-

Table S3. Associations of HLA amino acid residues with risk of RA in Asians and Europeans.

HLA	Amino acid position	Residue	Asian			European			F_{ST}	Imputation quality score (r^2 by SNP2HAP) in Asian RA studies		
			Frequency[a]		OR[b]	Frequency[a]		OR[b]				
			RA case	Control		RA case	Control			Chinese GWAS	Korean GWAS	Korean Immunochip
HLA-DRβ1	11	Val	0.346	0.192	2.16	0.470	0.182	3.78	0.000	0.96	0.99	1.00
		Asp	0.150	0.108	1.48	0.013	0.011	1.01	0.042	0.96	0.98	0.99
		Leu	0.068	0.056	1.22	0.145	0.113	1.30	0.011	1.00	1.00	1.00
		Pro	0.105	0.135	0.78	0.104	0.155	0.63	0.001	1.00	0.97	1.00
		Gly	0.048	0.075	0.69	0.064	0.133	0.49	0.009	0.97	0.99	0.99
		Ser	0.282	0.433	0.50	0.205	0.406	0.38	0.001	0.99	0.99	1.00
	13	His	0.308	0.175	2.03	0.449	0.174	3.71	0.000	0.96	1.00	1.00
		Phe	0.257	0.181	1.57	0.178	0.132	1.38	0.005	0.96	0.99	1.00
		Arg	0.105	0.135	0.78	0.104	0.155	0.62	0.001	1.00	0.97	1.00
		Tyr	0.048	0.075	0.69	0.064	0.133	0.49	0.009	0.97	0.99	0.98
		Gly	0.160	0.217	0.67	0.028	0.049	0.50	0.062	0.91	0.88	0.87
		Ser	0.121	0.216	0.49	0.176	0.357	0.40	0.024	0.89	0.88	0.88
	57	Ser	0.285	0.161	1.96	0.028	0.038	0.69	0.042	0.96	0.97	0.99
		Val	0.278	0.276	1.06	0.091	0.161	0.54	0.020	0.95	0.95	0.96
		Asp	0.411	0.510	0.66	0.869	0.776	1.88	0.077	0.94	0.94	0.95
		Ala	0.027	0.053	0.50	0.012	0.025	0.50	0.005	0.84	0.81	0.86
	71	Arg	0.820	0.744	1.56	0.458	0.487	0.97	0.070	0.96	0.99	0.99
		Lys	0.036	0.035	1.10	0.397	0.242	2.01	0.090	0.93	0.93	0.97
		Ala	0.095	0.122	0.77	0.092	0.142	0.59	0.001	0.98	1.00	0.99
		Glu	0.049	0.099	0.45	0.052	0.129	0.32	0.002	0.95	0.99	1.00
	74	Ala	0.628	0.558	1.34	0.801	0.664	2.10	0.012	0.94	0.96	0.95
		Glu	0.241	0.247	0.96	0.039	0.047	0.76	0.080	0.91	0.95	0.94
		Gln	0.049	0.076	0.70	0.064	0.133	0.49	0.009	0.97	0.99	1.00
		Leu	0.068	0.094	0.66	0.013	0.029	0.41	0.019	0.97	0.99	0.99
		Arg	0.014	0.026	0.54	0.082	0.128	0.59	0.037	1.00	0.99	0.99

Table S3. (Continued)

		Asp	0.006	0.003	4.21	0.130	0.118	2.14	0.058	1.00	1.00	1.00
B	9	His	0.204	0.174	1.06	0.227	0.212	0.95	0.002	0.98	0.99	1.00
		Tyr	0.790	0.822	0.91	0.643	0.670	0.82	0.031	0.98	0.99	1.00
		Phe	0.862	0.823	1.26	0.799	0.728	1.39	0.013	0.85	0.87	0.98
HLA-DPβ1	9	His	0.050	0.068	0.93	0.035	0.049	0.89	0.002	0.89	0.93	0.99
		Tyr	0.088	0.110	0.76	0.165	0.223	0.70	0.023	0.81	0.84	0.97

[a] Unadjusted allele frequencies of the HLA amino acid residues and the haplotypes. Haplotypes with frequency ≥0.005 in controls are indicated.

[b] Associations in HLA-B and HLA-DPβ1 were conditioned on the HLA-DRβ1 amino acid residues.

RA; rheumatoid arthritis, OR; odds ratio.

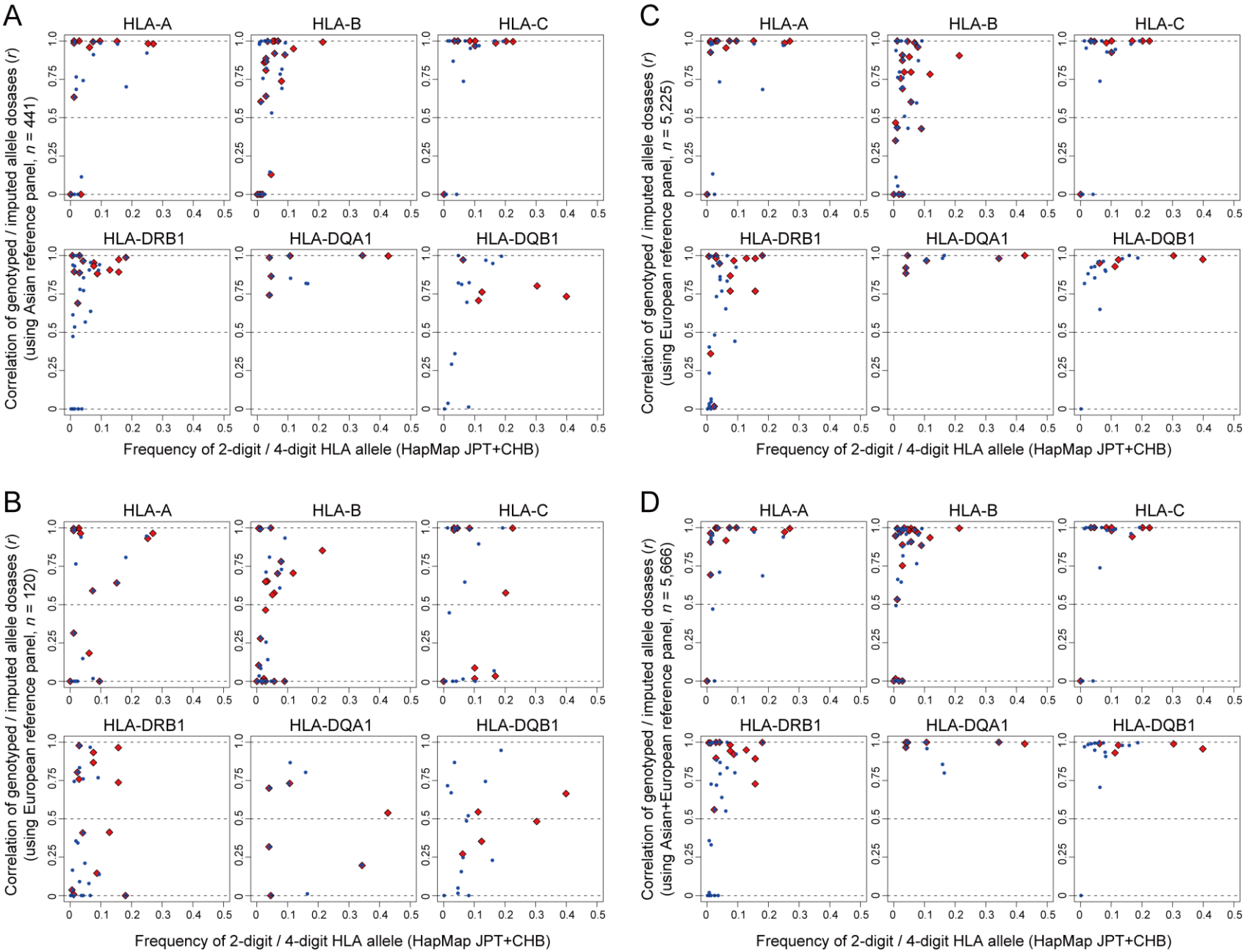
Table S4. Associations of HLA amino acid haplotypes with risk of RA in Asians (based on the model from the current Asian study).

HLA-DRβ1 amino acid position				Frequency[a]		RA risk association	
11	13	57	74	RA case	Control	OR (95%CI)	*P*
Val	His	Asp	Ala	0.025	0.011	3.42 (2.53-4.63)	1.2E-15
Val	His	Ser	Ala	0.226	0.090	2.97 (2.59-3.41)	3.3E-54
Val	Phe	Asp	Ala	0.038	0.017	2.77 (2.18-3.52)	1.1E-16
Asp	Phe	Val	Glu	0.149	0.108	1.77 (1.54-2.04)	3.9E-15
Leu	Phe	Asp	Ala	0.068	0.056	1.48 (1.24-1.76)	1.0E-05
Ser	Gly	Val	Ala	0.080	0.093	1.10 (0.94-1.30)	0.23
Pro	Arg	Asp	Ala	0.105	0.135	1.00 (1.00-1.00)	1.00
Ser	Gly	Ser	Leu	0.058	0.071	0.97 (0.82-1.16)	0.74
Val	His	Asp	Glu	0.057	0.074	0.93 (0.79-1.11)	0.43
Gly	Tyr	Val	Gln	0.048	0.075	0.88 (0.73-1.05)	0.16
Ser	Ser	Ala	Glu	0.013	0.020	0.78 (0.57-1.06)	0.107
Ser	Ser	Asp	Glu	0.008	0.012	0.74 (0.51-1.09)	0.13
Ser	Ser	Asp	Arg	0.013	0.026	0.69 (0.52-0.93)	0.015
Ser	Ser	Asp	Ala	0.085	0.156	0.67 (0.57-0.77)	1.1E-07
Ser	Gly	Ala	Glu	0.014	0.033	0.55 (0.41-0.72)	1.9E-05
Ser	Gly	Asp	Leu	0.008	0.022	0.42 (0.30-0.59)	9.4E-07

[a] Unadjusted allele frequencies of the HLA amino acid residues and the haplotypes. Haplotypes with frequency ≥0.005 in controls are indicated.

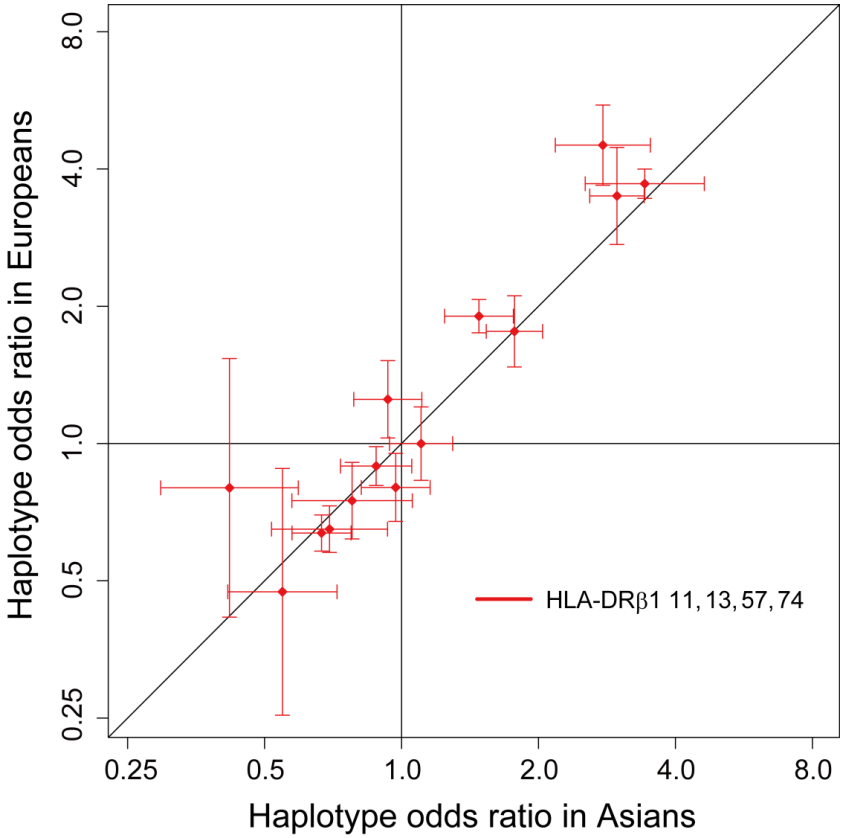
RA; rheumatoid arthritis, OR; odds ratio.

Figure S1. Imputation accuracy of the classical HLA alleles in Asians.



We empirically compared correlation of imputed and genotyped classical HLA allele dosages, using HapMap Phase II JPT+CHB dataset (*n* = 89). Each panel represents co-plots of frequencies and correlation coefficients (*r*) between imputed and genotyped 2-digit and 4-digit alleles of the 6 HLA genes (*HLA-A*, *B*, *C*, *DRB1*, *DQA1*, and *DQB1*). We conducted three sets of imputation using different reference panels; (**A**) Asian reference panel other than HapMap subjects (n = 441), (**B**) European reference panel from HapMap CEU founder populations (*n* = 120), (**C**) European reference panel from Type 1 Diabetes Genetics Consortium (T1DGC; *n* = 5,225), and (**D**) combined Asian and European reference panel (T1DGC for Europeans; *n* = 5,666)

Figure S2. Comparison of haplotype ORs of RA risk HLA amino acid polymorphisms between Asians and Europeans (based on the model from the current Asian study).



Odds ratios of the haplotypes consisting of the risk HLA amino acid polymorphisms based on the Asian model (HLA-DRβ1 amino acid positions 11, 13, 57, and 74) and their 95% confidence intervals are plotted based on those in Asians (*x*-axis) and Europeans (*y*-axis).