html; R statistical software, http://cran.r-project.org/; SNAP, http://www.broadinstitute.org/mpg/snap/index.php; NCBI GEO database, http://www.ncbi.nlm.nih.gov/geo/.

METHODS

Methods and any associated references are available in the online version of the paper at http://www.nature.com/naturegenetics/.

Note: Supplementary information is available on the Nature Genetics website.

ACKNOWLEDGMENTS

The authors acknowledge the essential role of the GARNET consortium in developing the study. In this study, the following GARNET members are included: CGM of RIKEN, University of Tokyo, the BioBank Japan Project, Kyoto University and IORRA. We would like to thank all the doctors and staff who participated in sample collection for the RIKEN cohort and the BioBank Japan Project. We thank K. Kobayashi and M. Kitazato for their technical assistance. We thank T. Raj for calculation of composite of multiple signals (CMS). We thank M. Kokubo for DNA extraction, GWAS genotyping and secretarial assistance. We would also like to thank H. Yoshifuji, N. Yukawa, D. Kawabata, T. Nojima, T. Usui and T. Fujii for collecting DNA samples. We thank Y. Katagiri for her technical efforts. We also appreciate the contribution of E. Inoue and other members of the Institute of Rheumatology, Tokyo Women's Medical University, for their efforts on the IORRA cohort. This study was supported in part by grants-in-aid from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) in Japan, the Ministry of Health, Labour and Welfare (MHLW) in Japan, the Japan Society for the Promotion of Science (JSPS), Core Research for Evolutional Science and Technology (CREST), Solution-Oriented Research for Science and Technology (SORST), INSERM and the Okawa Foundation for Information and Telecommunications.

AUTHOR CONTRIBUTIONS

Y. Okada, C.T., K.I., Y. Kochi and K.O. designed the study and drafted the manuscript. Y. Okada, C.T., K.I., T.K., H.O., N.N., M.T., M.L., K. Tokunaga and M.K. managed genotyping and manipulation of GWAS data. Y. Okada, Y. Kochi, C.T. and K.I. managed genotyping of replication cohorts. Y. Okada, T.K., H.O., E.A.S., A. Takahashi and R.Y. performed statistical analysis. Y. Kochi, A.S., K. Myouzen, T. Sawada, Y. Nishoka, M.Y., T. Matsubara, S.W., R.T. and S.T. collected samples and managed phenotype data for the rheumatoid arthritis cohorts from the BioBank Japan Project and CGM, RIKEN. C.T., K.O., T.K., M.T., K. Takasugi, K.S., A.M., S.H., K. Matsuo, H. Tanaka, K. Tajima and M.L. collected samples and managed phenotype data for the rheumatoid arthritis cohorts from Kyoto University. K.I., T. Suzuki, T.I., Y. Kawamura, H. Tanii, Y. Okazaki and T. Sakaki collected samples and managed phenotype data for the rheumatoid arthritis cohorts from IORRA. Y. Kochi managed the data for the SLE and Graves' disease cohorts. A.S., C.T. and K.I. analyzed the sera of subjects with rheumatoid arthritis. E.A.S., F.A.S.K., P.K.G., J.W., K.A.S., L.P. and R.M.P. managed the data for the rheumatoid arthritis cohorts in European populations. A. Taniguchi, A. Takahashi, K. Tokunaga, M.K., Y. Nakamura, N.K., T. Minori, R.M.P., H.Y., S.M., R.Y., F.M. and K.Y. supervised the overall study.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

Published online at http://www.nature.com/naturegenetics/.
Reprints and permissions information is available online at http://www.nature.com/reprints/index.html.

1. Suzuki, A. *et al.* Functional haplotypes of *PADI4*, encoding citrullinating enzyme peptidylarginine deiminase 4, are associated with rheumatoid arthritis. *Nat. Genet.* **34**, 395–402 (2003).
2. Kochi, Y. *et al.* A functional variant in *FCRL3*, encoding Fc receptor–like 3, is associated with rheumatoid arthritis and several autoimmunities. *Nat. Genet.* **37**, 478–485 (2005).
3. The Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* **447**, 661–678 (2007).
4. Remmers, E.F. *et al. STAT4* and the risk of rheumatoid arthritis and systemic lupus erythematosus. *N. Engl. J. Med.* **357**, 977–986 (2007).
5. Plenge, R.M. *et al. TRAF1–C5* as a risk locus for rheumatoid arthritis—a genomewide study. *N. Engl. J. Med.* **357**, 1199–1209 (2007).
6. Plenge, R.M. *et al.* Two independent alleles at 6q23 associated with risk of rheumatoid arthritis. *Nat. Genet.* **39**, 1477–1482 (2007).
7. Barton, A. *et al.* Rheumatoid arthritis susceptibility loci at chromosomes 10p15, 12q13 and 22q13. *Nat. Genet.* **40**, 1156–1159 (2008).
8. Suzuki, A. *et al.* Functional SNPs in *CD244* increase the risk of rheumatoid arthritis in a Japanese population. *Nat. Genet.* **40**, 1224–1229 (2008).
9. Gregersen, P.K. *et al. REL*, encoding a member of the NF-κB family of transcription factors, is a newly defined risk locus for rheumatoid arthritis. *Nat. Genet.* **41**, 820–823 (2009).
10. Kochi, Y. *et al.* A regulatory variant in *CCR6* is associated with rheumatoid arthritis susceptibility. *Nat. Genet.* **42**, 515–519 (2010).
11. Freudenberg, J. *et al.* Genome-wide association study of rheumatoid arthritis in Koreans: population-specific loci as well as overlap with European susceptibility loci. *Arthritis Rheum.* **63**, 884–893 (2011).
12. Terao, C. *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.* **20**, 2680–2685 (2011).
13. Raychaudhuri, S. *et al.* Common variants at *CD40* and other loci confer risk of rheumatoid arthritis. *Nat. Genet.* **40**, 1216–1223 (2008).
14. Raychaudhuri, S. *et al.* Genetic variants at *CD28*, *PRDM1* and *CD2/CD58* are associated with rheumatoid arthritis risk. *Nat. Genet.* **41**, 1313–1318 (2009).
15. Stahl, E.A. *et al.* Genome-wide association study meta-analysis identifies seven new rheumatoid arthritis risk loci. *Nat. Genet.* **42**, 508–514 (2010).
16. Zhernakova, A. *et al.* Meta-analysis of genome-wide association studies in celiac disease and rheumatoid arthritis identifies fourteen non-HLA shared loci. *PLoS Genet.* **7**, e1002004 (2011).
17. Kurreeman, F. *et al.* Genetic basis of autoantibody positive and negative rheumatoid arthritis risk in a multi-ethnic cohort derived from electronic health records. *Am. J. Hum. Genet.* **88**, 57–69 (2011).
18. Nakamura, Y. The BioBank Japan Project. *Clin. Adv. Hematol. Oncol.* **5**, 696–697 (2007).
19. Yamanaka, H. *et al.* Influence of methotrexate dose on its efficacy and safety in rheumatoid arthritis patients: evidence based on the variety of prescribing approaches among practicing Japanese rheumatologists in a single institute-based large observational cohort (IORRA). *Mod. Rheumatol.* **17**, 98–105 (2007).
20. Yamada, R. *et al.* Association between a single-nucleotide polymorphism in the promoter of the human interleukin-3 gene and rheumatoid arthritis in Japanese patients, and maximum-likelihood estimation of combinatorial effect that two genetic loci have on susceptibility to the disease. *Am. J. Hum. Genet.* **68**, 674–685 (2001).
21. Tokuhiro, S. *et al.* An intronic SNP in a RUNX1 binding site of *SLC22A4*, encoding an organic cation transporter, is associated with rheumatoid arthritis. *Nat. Genet.* **35**, 341–348 (2003).
22. Okada, Y. *et al.* A genome-wide association study identified *AFF1* as a susceptibility locus for systemic lupus eyrthematosus in Japanese. *PLoS Genet.* **8**, e1002455 (2012).
23. Stranger, B.E., Stahl, E.A. & Raj, T. Progress and promise of genome-wide association studies for human complex trait genetics. *Genetics* **187**, 367–383 (2011).
24. Shimane, K. *et al.* A single nucleotide polymorphism in the *IRF5* promoter region is associated with susceptibility to rheumatoid arthritis in the Japanese patients. *Ann. Rheum. Dis.* **68**, 377–383 (2009).

[1]Laboratory for Autoimmune Diseases, Center for Genomic Medicine (CGM), RIKEN, Yokohama, Japan. [2]Department of Allergy and Rheumatology, Graduate School of Medicine, University of Tokyo, Tokyo, Japan. [3]Laboratory for Statistical Analysis, CGM, RIKEN, Yokohama, Japan. [4]Center for Genomic Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan. [5]Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, Kyoto, Japan. [6]Institute of Rheumatology, Tokyo Women's Medical University, Tokyo, Japan. [7]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA. [8]Broad Institute, Cambridge, Massachusetts, USA. [9]Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands. [10]Department of Human Genetics, Graduate School of Medicine, University of Tokyo, Tokyo, Japan. [11]Department of Rheumatology, Tokyo Medical University Hospital, Tokyo, Japan. [12]Yamanashi Prefectural Central Hospital, Yamanashi, Japan. [13]Department of Orthopaedic Surgery, Yukioka Hospital, Osaka, Japan. [14]Matsubara Mayflower Hospital, Hyogo, Japan. [15]Osaka Minami National Hospital, Osaka, Japan. [16]Department of Orthopedic Surgery, Tottori University, Tottori, Japan. [17]Department of Rheumatology, National Hospital Organization, Sagamihara Hospital, Kanagawa, Japan. [18]Center for Rheumatic Diseases, Dohgo Spa Hospital, Ehime, Japan. [19]Department of Rheumatology, Niigata Rheumatic Center, Niigata, Japan. [20]Saiseikai Takaoka Hospital, Toyama, Japan. [21]Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, Aichi, Japan. [22]Aichi Cancer Center Hospital and Research Institute, Aichi, Japan. [23]Department of Orthopaedic Surgery, Keio University, Tokyo, Japan. [24]Yokohama Clinic, Warakukai Medical Corporation, Yokohama, Japan. [25]Department of Psychiatry, Mie University School of Medicine, Mie, Japan. [26]Metropolitan Matsuzawa Hospital, Tokyo, Japan. [27]Graduate School of Education, University of Tokyo, Tokyo, Japan. [28]The Feinstein Institute for Medical Research, North Shore–Long Island Jewish Health System, Manhasset, New York, USA. [29]Rheumatology Unit,

Department of Medicine in Solna, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden. [30]Arthritis Research Campaign–Epidemiology Unit, The University of Manchester, Manchester Academic Health Science Centre, Manchester, UK. [31]Division of Medicine, University of Toronto, Mount Sinai Hospital and University Health Network, Toronto, Ontario, Canada. [32]Commisariat a l'Energie Atomique (CEA), Institut Genomique, Centre National de Genotypage, Evry, France. [33]Fondation Jean Dausset, Centre d'Etude du Polymorphisme Humain, Paris, France. [34]Laboratory for Genotyping Development, CGM, RIKEN, Yokohama, Japan. [35]Laboratory of Molecular Medicine, Human Genome Center, Institute of Medical Science, University of Tokyo, Tokyo, Japan. [36]Laboratory for International Alliance, CGM, RIKEN, Yokohama, Japan. [37]Unit of Statistical Genetics, Center for Genomic Medicine Graduate School of Medicine Kyoto University, Kyoto, Japan. [38]Core Research for Evolutional Science and Technology (CREST) Program, Japan Science and Technology Agency, Kawaguchi, Japan. [39]Institut National de la Santé et de la Recherche Médicale (INSERM), Unité U852, Kyoto University Graduate School of Medicine, Kyoto, Japan. [40]These authors contributed equally to this work. [41]These authors jointly directed this work. Correspondence should be addressed to Y.K. (ykochi@src.riken.jp) or K.O. (ohmurako@kuhp.kyoto-u.ac.jp).

ONLINE METHODS

Subjects. The Japanese participants in the meta-analysis (4,074 rheumatoid arthritis cases and 16,891 controls) and the replication study (5,277 rheumatoid arthritis cases and 21,684 controls) were obtained through the collaborations of the GARNET consortium (**Supplementary Table 1**)[10,12]. The meta-analysis was conducted on three independent GWAS (from the BioBank Japan Project[18] with 2,414 rheumatoid arthritis cases and 14,245 controls[10], Kyoto University with 1,237 rheumatoid arthritis cases and 2,087 controls[12] and IORRA[19] with 423 rheumatoid arthritis cases and 559 controls). The replication study consisted of two independent cohorts (cohort 1 included 3,830 rheumatoid arthritis cases and 17,920 controls, and cohort 2 included 1,447 rheumatoid arthritis cases and 3,764 controls). We employed a case-control cohort of SLE (891 cases and 3,384 controls)[22] and 1,783 cases with Graves' disease[10]. Details of 5,539 rheumatoid arthritis cases and 20,169 controls included in the meta-analysis in European populations were described elsewhere[15]. All participants provided written informed consent for participation in the study, as approved by the ethical committees of the institutional review boards. Detailed descriptions of the participating subjects are provided (**Supplementary Note**).

Genotyping and quality control in the GWAS. Genotyping platforms and quality control criteria for the GWAS, including cutoff values for sample call rates, SNP call rates, MAF and Hardy-Weinberg P values, are given (**Supplementary Table 2**). For the subjects enrolled in each of three GWAS, we excluded closely related subjects with first- or second-degree kinship, which was estimated using PLINK version 1.06 (see URLs). We also excluded the subjects determined to be ancestry outliers from East Asian populations using PCA performed by EIGENSTRAT version 2.0 (see URLs) along with HapMap Phase 2 panels (release 24; **Supplementary Fig. 1**). Genotype imputation was performed on the basis of the HapMap Phase 2 East Asian populations, using MACH version 1.0.16 (see URLs) in a two-step procedure as described elsewhere[25]. We excluded imputed SNPs with MAF < 0.01 or $Rsq < 0.5$ from each of the GWAS. Associations of the SNPs with rheumatoid arthritis were assessed by logistic regression models assuming additive effects of the allele dosages of the SNPs using mach2dat software (see URLs).

Meta-analysis. We included 1,948,139 autosomal SNPs that satisfied quality control criteria in all three GWAS (**Supplementary Table 2**). SNP information was based on a forward strand of the NCBI build 36.3 reference sequence. The meta-analysis was performed using an inverse variance method assuming a fixed-effects model from the study-specific effect sizes (logarithm of odds ratio) and the standard errors of the coded alleles of the SNPs determined with the Java source code implemented by the authors[25]. Genomic control corrections[26] were carried out on test statistics of the GWAS using the study-specific inflation factor (λ_{GC}) and was applied or reapplied to the results of our current meta-analysis (**Supplementary Fig. 2**).

Replication study. We selected a SNP for the replication study from each of the loci that exhibited $P < 5.0 \times 10^{-4}$ in the meta-analysis that had not previously been reported as rheumatoid arthritis susceptibility loci[1–16] (**Supplementary Table 3**). For control subjects, we used genotype data obtained from additional GWAS for non-autoimmune diseases or healthy controls, genotyped using Illumina HumanHap550 BeadChips or HumanHap610-Quad BeadChips, and the cases for rheumatoid arthritis and Graves' disease were genotyped with the TaqMan genotyping system (Applied Biosystems; **Supplementary Table 1**). Selection of the SNP was conducted according to the following criteria: if the SNP with the most significant association in the locus was genotyped in the replication control panel, then that SNP was selected; otherwise, a tag SNP in the replication control panel with the strongest LD was selected (mean $r^2 = 0.89$). For the three SNPs that yielded low call rates (<90%), we alternatively selected proxy SNPs with the second strongest LD. As a result, average genotyping call rates of the SNPs were 99.9% and 99.0% for the controls and cases, respectively. We then evaluated concordance rates between the assayed genotypes by applying these two different methods to samples from 376 subjects who were randomly selected. This procedure yielded high concordance rates of ≥99.9%. Associations of the SNPs were evaluated using logistic regression assuming an additive-effects model of genotypes in R statistical software version 2.11.0 (see URLs). The combined study of the meta-analysis and replication study was performed using an inverse variance method assuming a fixed-effects model[25].

***Cis* eQTL analysis.** For each marker SNP of the newly identified rheumatoid arthritis susceptibility locus, correlations between SNP genotypes and expression levels of genes located 300 kb upstream or downstream of the SNP measured in B-lymphoblastoid cell lines (GSE6536) were evaluated using data from the HapMap Phase 2 east Asian populations[27].

Multi-ancestry analysis of the meta-analyses in Japanese and Europeans. We evaluated the associations of the variants in the validated rheumatoid arthritis susceptibility loci by comparing the results from the current meta-analysis in Japanese with those from a previous meta-analysis in Europeans[15]. We assessed two variants in the *IRF5* locus, where different causal variants were identified in the two populations[24]. For the conditional analysis of the regional associations in the *ARID5B* locus (**Supplementary Fig. 3**), we repeated the meta-analysis at that locus by incorporating genotypes of the referenced SNP(s) as additional covariate(s). For comparison of the odds ratios of the SNPs, we first selected SNPs that were shared between the meta-analyses in Japanese and Europeans. Next, we removed the SNPs located more than 1 Mb away from each of the marker SNPs in the validated rheumatoid arthritis susceptibility loci, except for in the HLA region, where we removed the SNPs located between 24,000,000 bp to 36,000,000 bp on chromosome 6 because of the existence of long-range haplotypes with rheumatoid arthritis susceptibility in this region[28]. LD pruning of the SNPs was conducted for the SNP pairs that were in LD ($r^2 \geq 0.3$) in both HapMap Phase 2 East Asian and Utah residents of Northern and Western European ancestry (CEU) populations (release 24). Correlations of the odds ratios were evaluated using R statistical software version 2.11.0.

25. Okada, Y. *et al.* Identification of nine novel loci associated with white blood cell subtypes in a Japanese population. *PLoS Genet.* **7**, e1002067 (2011).
26. de Bakker, P.I. *et al.* Practical aspects of imputation-driven meta-analysis of genome-wide association studies. *Hum. Mol. Genet.* **17**, R122–R128 (2008).
27. Stranger, B.E. *et al.* Population genomics of human gene expression. *Nat. Genet.* **39**, 1217–1224 (2007).
28. Okada, Y. *et al.* Contribution of a haplotype in the HLA region to anti–cyclic citrullinated peptide antibody positivity in rheumatoid arthritis, independently of HLA-DRB1. *Arthritis Rheum.* **60**, 3582–3590 (2009).

Supplementary Information

Meta-analysis identifies nine new loci associated with rheumatoid arthritis in the Japanese population

Yukinori Okada, Chikashi Terao, Katsunori Ikari, Yuta Kochi, Koichiro Ohmura, Akari Suzuki, Takahisa Kawaguchi, Eli A. Stahl, Fina Kurreman, Nao Nishida, Hiroko Ohmiya, Keiko Myouzen, Meiko Takahashi, Tetsuji Sawada, Yuichi Nishioka, Masao Yukioka, Tsukasa Matsubara, Shigeyuki Wakitani, Ryota Teshima, Shigeto Tohma, Kiyoshi Takasugi, Kota Shimada, Akira Murasawa, Shigeru Honjo, Keitaro Matsuo, Hideo Tanaka, Kazuo Tajima, Taku Suzuki, Takuji Iwamoto, Yoshiya Kawamura, Hisashi Tanii, Yuji Okazaki, Tsukasa Sasaki, Peter K. Gregersen, Leonid Padyukov, Jane Worthington, Katherine A. Siminovitch, Mark Lathrop, Atsuo Taniguchi, Atsushi Takahashi, Katsushi Tokunaga, Michiaki Kubo, Yusuke Nakamura, Naoyuki Kamatani, Tsuneyo Mimori, Robert M. Plenge, Hisashi Yamanaka, Shigeki Momohara, Ryo Yamada, Fumihiko Matsuda, and Kazuhiko Yamamoto

*Correspondence authors: Yuta Kochi and Koichiro Ohmura

Yuta Kochi, MD, PhD

Laboratory for Autoimmune diseases, Center for Genomic Medicine, RIKEN

7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

Telephone: +81-3-5800-8828, Fax: +81-3-5800-8828

E-mail: ykochi@src.riken.jp

Koichiro Ohmura, MD, PhD

Department of Rheumatology and Clinical immunology, Graduate School of Medicine, Kyoto University

54 Kawaharacho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan

Telephone: +81-75-751-4380; Fax: +81-75-751-4338

Email: ohmurako@kuhp.kyoto-u.ac.jp

Supplementary Tables

Supplementary Figures

Supplementary Note

Supplementary Table 1. Characteristics of the cohorts enrolled in the study.

Disease	Stage	Cohort	Genotyping platform	No. subjects	Female	Age (mean±SD)	Auto-antibody positivity
Rheumatoid arthritis	GWAS meta-analysis	BioBank Japan Project	Illumina HumanHap610-Quad BeadChip	2,414	81.0%	61.5 ± 11.9	anti-CCP: 79.2%, RF: 75.7%
		Kyoto University	Illumina HumanHap300 BeadChip Illumina Human CNV370-Duo BeadChip Illumina HumanHap610-Quad BeadChip	1,237	80.1%	60.8 ± 12.2	anti-CCP: 85.2%, RF: 85.9%
		IORRA	Affymetrix Genome-wide Human SNP Array 6.0	423	81.3%	58.1 ± 12.1	anti-CCP: 86.6%, RF: 88.2%
	Replication study 1	BioBank Japan Project, RIKEN, IORRA	Taqman genotyping system	3,830	91.3%	60.6 ± 12.3	anti-CCP: 80.6%, RF: 86.3%
	Replication study 2	Kyoto University	Taqman genotyping system	1,447	82.1%	61.7 ± 12.6	anti-CCP: 82.9%, RF: 85.2%
Systemic lupus erythematosus	-	ADSG	Illumina HumanHap610-Quad BeadChip	891	88.1%	43.6 ± 13.9	-
Graves' disease	-	BioBank Japan Project	Taqman genotyping system	1,783	72.2%	48.6 ± 15.3	-
Control subjects	GWAS meta-analysis	BioBank Japan Project	Illumina HumanHap610-Quad BeadChip	14,245	44.3%	63.1 ± 12.2	-
		Kyoto University	Illumina HumanHap550 BeadChip Illumina HumanHap610-Quad BeadChip	2,087	44.4%	51.3 ± 15.3	-
		IORRA	Affymetrix Genome-wide Human SNP Array 6.0	559	61.2%	39.9 ± 10.9	-
	Replication study 1	BioBank Japan Project	Illumina HumanHap550 BeadChip Illumina HumanHap610-Quad BeadChip	17,920	48.0%	59.7 ± 14.2	-
	Replication study 2	Kyoto University	Illumina HumanHap550 BeadChip Illumina HumanHap610-Quad BeadChip	3,764	50.5%	57.2 ± 14.4	-

GWAS, genome-wide association study; SD, standard deviation; RF, rheumatoid factor; anti-CCP; anti-cyclic citrullinated peptide antibody.

Supplementary Table 2. Genotyping and imputation methods in the GWAS enrolled in the meta-analysis.

Cohort	No. subjects		GWAS QC criteria				Imputation method				No. SNPs after QC		Inflation factor
	RA cases	Controls	Sample call rate	SNP call rate	MAF[a]	HWE *P*-value[b]	Software	Reference	MAF	Quality score	GWAS	Imputed	
BioBank Japan Project	2,414	14,245	> 0.98	> 0.99	> 0.01	> 10^{-7}	MACH v1.0.16	HapMap Phase II (rel24), JPT+CHB	> 0.01	*Rsq* >0.5	477,784	2,263,308	1.061
Kyoto University	1,237	2,087	> 0.90[c]	> 0.95[c]	> 0.05	> 10^{-7}	MACH v1.0.16	HapMap Phase II (rel24), JPT+CHB	> 0.01	*Rsq* >0.5	228,622[d]	1,986,176	1.116
IORRA	423	559	> 0.95	> 0.98	> 0.05	> 10^{-6}	MACH v1.0.16	HapMap Phase II (rel24), JPT+CHB	> 0.01	*Rsq* >0.5	473,168	2,197,793	1.020
GWAS meta-analysis	4,074	16,891	-	-	-	-	-	-	-	-	-	1,948,139[e]	1.036

[a]Assessed in RA cases and controls, respectively.

[b]Assessed in controls.

[c]Assessed for each of the genotyping platforms, separately.

[d]SNPs that were shared among all the genotyping platforms were enrolled.

[e]SNPs that satisfied MAF > 0.01 and *Rsq* > 0.5 in all the GWAS were enrolled.

GWAS, genome-wide association study; QC, quality control; RA, rheumatoid arthritis; MAF, minor allele frequency; HWE, Hardy-Weinberg equilibrium.

Supplementary Table 3. Results of the replication study for the loci identified in the GWAS meta-analysis of rheumatoid arthritis.

rsID[a]	Chr	Position (bp)	Cyto-band	Gene(s)	Allele 1/2	GWAS meta-analysis				Replication study 1				Replication study 2				Combined study	
						Allele 1 Freq.		OR (95%CI)[b]	P	Allele 1 Freq.		OR (95%CI)[b]	P	Allele 1 Freq.		OR (95%CI)[b]	P	OR (95%CI)[b]	P
						RA	Control			RA	Control			RA	Control				
rs2236395	1	2,436,740	1p36	*TNFRSF14*	A/G	0.58	0.55	1.12 (1.06-1.18)	2.5E-05	0.56	0.55	1.06 (1.01-1.11)	2.9E-02	0.54	0.55	0.97 (0.89-1.06)	4.7E-01	1.07 (1.03-1.11)	6.3E-05
rs7519611	1	42,388,229	1p34	*GUCA2B*	T/C	0.60	0.58	1.12 (1.06-1.18)	7.1E-05	0.59	0.59	1.02 (0.97-1.07)	5.5E-01	0.58	0.58	1.01 (0.93-1.10)	8.1E-01	1.05 (1.02-1.09)	1.8E-03
rs4328027	1	54,689,944	1p32	*SSBP3*	C/T	0.69	0.67	1.14 (1.08-1.21)	5.4E-06	0.68	0.67	1.02 (0.97-1.08)	4.6E-01	0.68	0.66	1.09 (0.99-1.20)	7.2E-02	1.08 (1.04-1.12)	2.7E-05
rs4845624	1	150,094,437	1q21	*THEM5-THEM4*	G/A	0.42	0.40	1.10 (1.05-1.16)	2.9E-04	0.41	0.40	1.03 (0.98-1.08)	2.8E-01	0.40	0.40	1.01 (0.92-1.10)	9.0E-01	1.06 (1.02-1.09)	1.5E-03
rs11900673	2	62,306,165	2p15	*B3GNT2*	T/C	0.31	0.28	1.15 (1.08-1.21)	3.5E-06	0.31	0.29	1.10 (1.04-1.16)	7.1E-04	0.29	0.28	1.05 (0.95-1.15)	3.3E-01	1.11 (1.07-1.15)	1.1E-08
rs2418896	2	71,289,777	2p13	*PAIP2B-ZNF638*	G/A	0.23	0.22	1.14 (1.07-1.21)	5.8E-05	0.23	0.23	1.02 (0.96-1.09)	4.4E-01	0.22	0.21	1.08 (0.97-1.20)	1.5E-01	1.08 (1.04-1.12)	1.8E-04
rs1864548	2	79,543,080	2p12	*CTNNA2*	C/T	0.29	0.26	1.15 (1.09-1.22)	1.5E-06	0.29	0.28	1.01 (0.96-1.07)	6.0E-01	0.28	0.28	1.00 (0.91-1.10)	9.7E-01	1.07 (1.03-1.11)	3.7E-04
rs155399	3	1,361,467	3p26	*CNTN6*	C/T	0.21	0.19	1.14 (1.07-1.22)	7.4E-05	0.21	0.21	1.03 (0.97-1.10)	3.0E-01	0.21	0.21	1.02 (0.92-1.14)	7.0E-01	1.07 (1.03-1.12)	5.5E-04
rs4130687	3	29,419,115	3p24	*RBMS3*	G/A	0.12	0.10	1.20 (1.10-1.29)	2.2E-05	0.10	0.11	0.97 (0.90-1.06)	5.2E-01	0.10	0.10	1.01 (0.87-1.16)	9.4E-01	1.07 (1.01-1.13)	1.2E-02
rs2901755	3	173,167,209	3q26	*TMEM212-FNDC3B*	A/G	0.42	0.40	1.12 (1.06-1.18)	6.5E-05	0.42	0.41	1.04 (0.99-1.09)	1.6E-01	0.41	0.42	0.96 (0.88-1.04)	3.1E-01	1.06 (1.02-1.09)	1.5E-03
rs291928	3	175,210,677	3q26	*NLGN1*	A/G	0.08	0.07	1.22 (1.11-1.34)	8.3E-05	0.07	0.07	1.10 (1.00-1.21)	5.8E-02	0.06	0.06	1.00 (0.83-1.20)	9.9E-01	1.14 (1.07-1.21)	6.9E-05
rs17462424	4	47,293,055	4p12	*ATP10D-DORIN*	C/T	0.21	0.19	1.14 (1.07-1.22)	4.8E-05	0.19	0.19	0.98 (0.92-1.05)	5.8E-01	0.18	0.19	0.98 (0.88-1.09)	7.2E-01	1.05 (1.01-1.09)	2.2E-02
rs2867461	4	79,732,239	4q21	*ANXA3*	A/G	0.46	0.44	1.13 (1.08-1.19)	4.7E-06	0.47	0.45	1.12 (1.07-1.18)	5.4E-06	0.47	0.44	1.13 (1.04-1.23)	6.4E-03	1.13 (1.09-1.17)	1.2E-12
rs295208	5	94,347,865	5q15	*MCTP1*	T/C	0.38	0.36	1.12 (1.06-1.18)	4.0E-05	0.36	0.36	0.97 (0.93-1.03)	3.3E-01	0.37	0.37	0.99 (0.91-1.08)	8.4E-01	1.04 (1.00-1.07)	4.3E-02
rs657075	5	131,458,017	5q31	*CSF2*	A/G	0.38	0.36	1.12 (1.06-1.18)	3.2E-05	0.38	0.36	1.12 (1.06-1.18)	1.9E-05	0.37	0.35	1.09 (0.99-1.19)	6.8E-02	1.12 (1.08-1.15)	2.8E-10
rs9405675	6	389,600	6p25	*IRF4-EXOC2*	A/G	0.41	0.39	1.11 (1.05-1.17)	1.4E-04	0.40	0.39	1.02 (0.97-1.08)	3.8E-01	0.42	0.38	1.17 (1.07-1.27)	6.5E-04	1.08 (1.04-1.12)	9.6E-06
rs12529514	6	14,204,637	6p23	*CD83*	C/T	0.16	0.14	1.19 (1.10-1.27)	6.8E-06	0.16	0.15	1.10 (1.03-1.18)	5.0E-03	0.16	0.15	1.13 (1.00-1.27)	4.6E-02	1.14 (1.09-1.19)	2.0E-08
rs2233434	6	44,340,898	6p21.1	*NFKBIE*	G/A	0.24	0.21	1.23 (1.16-1.31)	9.2E-11	0.24	0.22	1.15 (1.08-1.21)	4.7E-06	0.25	0.21	1.23 (1.11-1.37)	5.1E-05	1.19 (1.15-1.24)	5.8E-19
rs725351	6	91,175,642	6q15	*MACH2-MAP3K7*	C/T	0.48	0.45	1.12 (1.06-1.17)	4.5E-05	0.46	0.45	1.02 (0.97-1.08)	3.6E-01	0.48	0.46	1.09 (1.00-1.18)	5.5E-02	1.07 (1.04-1.11)	4.7E-05
rs7752089	6	150,202,127	6q25	*LRP11*	A/G	0.30	0.27	1.14 (1.08-1.21)	8.6E-06	0.29	0.27	1.09 (1.03-1.15)	2.5E-03	0.26	0.28	0.89 (0.81-0.99)	2.4E-02	1.08 (1.04-1.12)	3.3E-05
rs10487790	7	15,009,432	7p21	*DGKB-TMEM195*	C/T	0.16	0.15	1.15 (1.07-1.23)	1.7E-04	0.16	0.15	1.04 (0.97-1.12)	2.3E-01	0.15	0.15	0.99 (0.88-1.12)	9.1E-01	1.08 (1.03-1.13)	1.1E-03
rs7808716	7	52,169,565	7p12	*LOC100131871*	G/A	0.56	0.54	1.12 (1.06-1.17)	4.4E-05	0.56	0.55	1.05 (1.00-1.10)	5.1E-02	0.56	0.55	1.04 (0.96-1.14)	3.3E-01	1.08 (1.04-1.11)	1.1E-05
rs4878117	9	89,475,284	9q21	*DAPK1*	C/T	0.53	0.51	1.10 (1.05-1.16)	2.8E-04	0.51	0.51	0.99 (0.95-1.04)	8.1E-01	0.50	0.51	0.97 (0.89-1.05)	4.4E-01	1.03 (1.00-1.07)	4.8E-02
rs1750734	10	11,201,984	10p14	*CUGBP2*	G/A	0.88	0.87	1.20 (1.10-1.30)	2.2E-05	0.87	0.86	1.06 (0.98-1.14)	1.4E-01	0.88	0.87	1.07 (0.94-1.22)	3.0E-01	1.11 (1.06-1.17)	3.2E-05
rs10821944	10	63,455,095	10q21	*ARID5B*	G/T	0.39	0.36	1.17 (1.11-1.23)	1.0E-08	0.40	0.36	1.15 (1.09-1.20)	1.5E-07	0.38	0.34	1.17 (1.07-1.28)	4.8E-04	1.16 (1.12-1.20)	5.5E-18
rs7911085	10	81,675,250	10q22	*MBL1P1-SFTPD*	A/G	0.26	0.23	1.17 (1.10-1.24)	9.9E-07	0.25	0.24	1.04 (0.98-1.10)	1.9E-01	0.24	0.24	0.96 (0.87-1.06)	4.1E-01	1.08 (1.04-1.12)	1.4E-04
rs7905501	10	94,830,706	10q23	*EXOC6-CYP26A1*	T/C	0.09	0.07	1.24 (1.13-1.36)	1.1E-05	0.08	0.08	0.96 (0.87-1.05)	3.8E-01	0.08	0.07	1.17 (1.00-1.37)	4.4E-02	1.10 (1.04-1.17)	1.3E-03
rs4255548	11	68,730,546	11q13	*MYEOV*	G/A	0.50	0.47	1.11 (1.06-1.17)	9.2E-05	0.47	0.47	1.00 (0.95-1.06)	8.9E-01	0.49	0.47	1.05 (0.96-1.15)	2.5E-01	1.05 (1.02-1.09)	1.8E-03
rs3781913	11	72,051,144	11q13	*PDE2A-ARAP1*	T/G	0.71	0.69	1.11 (1.05-1.17)	3.2E-04	0.72	0.69	1.12 (1.06-1.18)	4.6E-05	0.73	0.70	1.15 (1.05-1.27)	3.8E-03	1.12 (1.08-1.16)	5.8E-10
rs4937362	11	127,997,949	11q24	*ETS1-FLI1*	T/C	0.71	0.68	1.13 (1.07-1.19)	2.0E-05	0.69	0.68	1.06 (1.00-1.12)	4.0E-02	0.70	0.68	1.10 (1.00-1.21)	5.4E-02	1.09 (1.06-1.13)	7.5E-07
rs10876864	12	54,687,352	12q13	*IKZF4-RPS26*	A/G	0.83	0.81	1.14 (1.07-1.22)	1.5E-04	0.82	0.81	1.03 (0.97-1.10)	3.5E-01	0.81	0.80	1.06 (0.95-1.18)	3.2E-01	1.08 (1.03-1.12)	4.4E-04
rs4943253	13	34,245,598	13q13	*NBEA*	A/G	0.44	0.41	1.12 (1.07-1.18)	1.8E-05	0.42	0.41	1.04 (0.99-1.09)	1.4E-01	0.42	0.41	1.04 (0.95-1.14)	3.7E-01	1.07 (1.04-1.11)	3.0E-05
rs17103212	14	34,878,995	14q13	*PSMA6-NFKBIA*	C/T	0.90	0.88	1.22 (1.12-1.33)	1.5E-05	0.88	0.89	0.98 (0.91-1.06)	6.6E-01	0.88	0.87	1.11 (0.97-1.27)	1.2E-01	1.09 (1.03-1.14)	2.2E-03
rs3783637	14	54,417,868	14q22	*GCH1*	C/T	0.76	0.74	1.13 (1.07-1.20)	6.5E-05	0.76	0.75	1.05 (1.00-1.12)	6.9E-02	0.75	0.72	1.12 (1.02-1.23)	2.2E-02	1.10 (1.06-1.14)	2.0E-06
rs1957895	14	60,978,085	14q23	*PRKCH*	G/T	0.40	0.39	1.12 (1.06-1.18)	4.1E-05	0.41	0.40	1.08 (1.03-1.14)	1.5E-03	0.40	0.39	1.03 (0.94-1.12)	5.2E-01	1.09 (1.05-1.13)	3.6E-07
rs2841277	14	104,462,050	14q32	*PLD4*	T/C	0.72	0.69	1.11 (1.05-1.18)	2.8E-04	0.72	0.68	1.18 (1.12-1.25)	4.1E-09	0.72	0.69	1.19 (1.08-1.30)	4.2E-04	1.15 (1.11-1.19)	1.9E-14
rs961090	15	38,404,706	15q15	*PLCB2*	C/T	0.86	0.84	1.15 (1.07-1.24)	2.3E-04	0.85	0.84	1.07 (1.00-1.15)	4.3E-02	0.85	0.85	0.99 (0.88-1.11)	8.0E-01	1.09 (1.04-1.14)	2.4E-04
rs6496667	15	88,694,672	15q26	*ZNF774*	A/C	0.38	0.35	1.13 (1.07-1.19)	4.7E-05	0.38	0.36	1.08 (1.03-1.14)	1.9E-03	0.36	0.36	1.01 (0.92-1.11)	8.2E-01	1.09 (1.05-1.13)	1.4E-06
rs7498915	16	17,427,348	16p12	*XYLT1*	T/C	0.95	0.93	1.28 (1.14-1.44)	6.6E-05	0.93	0.92	1.07 (0.98-1.18)	1.5E-01	0.93	0.92	1.09 (0.92-1.28)	3.3E-01	1.14 (1.06-1.22)	1.6E-04
rs7404928	16	23,796,341	16p12	*PRKCB1*	T/C	0.65	0.62	1.13 (1.07-1.19)	1.5E-05	0.64	0.62	1.07 (1.01-1.12)	1.6E-02	0.64	0.64	1.01 (0.93-1.11)	7.9E-01	1.08 (1.05-1.12)	4.0E-06
rs2280381	16	84,576,134	16q24	*IRF8*	T/C	0.86	0.84	1.16 (1.08-1.25)	1.0E-04	0.85	0.83	1.10 (1.03-1.17)	7.0E-03	0.84	0.84	1.06 (0.94-1.19)	3.4E-01	1.12 (1.07-1.17)	2.4E-06
rs2290400	17	35,319,766	17q12	*IKZF3-ZPBP2-GSDML-ORMDL3 -GSDM1-PSMD3-CSF3*	C/T	0.28	0.26	1.12 (1.05-1.18)	2.8E-04	0.27	0.27	1.01 (0.96-1.07)	6.8E-01	0.30	0.27	1.13 (1.03-1.25)	1.1E-02	1.07 (1.03-1.11)	2.3E-04
rs9908256	17	40,406,871	17q21	*C1QL1*	C/T	0.59	0.57	1.11 (1.05-1.17)	1.8E-04	0.58	0.58	1.01 (0.96-1.07)	6.0E-01	0.56	0.58	0.92 (0.85-1.01)	7.6E-02	1.04 (1.00-1.07)	3.3E-02
rs4328484	17	66,627,825	17q24	no gene	A/G	0.65	0.62	1.13 (1.07-1.19)	1.3E-05	0.62	0.62	0.99 (0.94-1.04)	5.6E-01	0.62	0.62	1.00 (0.91-1.09)	9.6E-01	1.04 (1.01-1.08)	1.2E-02
rs2847297	18	12,787,694	18p11	*PTPN2*	G/A	0.37	0.33	1.16 (1.11-1.23)	3.5E-08	0.36	0.35	1.02 (0.97-1.08)	3.9E-01	0.39	0.35	1.17 (1.07-1.28)	5.0E-04	1.10 (1.07-1.14)	2.2E-08
rs1284427	18	13,620,634	18p11	*C18orf1*	G/A	0.52	0.49	1.11 (1.06-1.17)	8.7E-05	0.49	0.50	0.96 (0.92-1.01)	1.4E-01	0.51	0.51	1.00 (0.92-1.09)	9.8E-01	1.03 (1.00-1.06)	9.3E-02
rs12625311	20	51,270,200	20q13	*TSHZ2*	C/T	0.36	0.34	1.12 (1.06-1.18)	6.4E-05	0.33	0.34	0.95 (0.90-1.00)	5.1E-02	0.34	0.33	1.04 (0.95-1.13)	4.5E-01	1.03 (0.99-1.07)	9.8E-02

[a]Based on forward strand and NCBI Build 36.3. Selection criteria of the SNPs in the replication studies are described in **ONLINE METHODS**.

[b]Odds ratio of allele 1.

GWAS, genome-wide association study; RA, rheumatoid arthritis; OR, odds ratio; 95%CI, 95% confidence interval.

Supplementary Table 4. Results of cis-expression quantitative trait locus (cis-eQTL) analysis in the novel rheumatoid arthritis loci.

rsID[a]	Chr	Position (bp)	Cyto-band	Gene	No. cis-probes[b]	Smallest cis-eQTL P[c]	Corrected cis-eQTL P[d]	Cis-eQTL probe[e]	Cis-eQTL gene[e]
rs11900673	2	62,306,165	2p15	*B3GNT2*	3	0.29	0.88	-	-
rs2867461	4	79,732,239	4q21	*ANXA3*	4	0.20	0.82	-	-
rs657075	5	131,458,017	5q31	*CSF2*	11	7.2×10^{-4}	0.0079	GI_4758867-S	*P4HA2*
rs12529514	6	14,204,637	6p23	*CD83*	6	0.19	1	-	-
rs2233434	6	44,340,898	6p21.1	*NFKBIE*	14	0.0021	0.030	GI_38569416-S	*AARS2*
rs10821944	10	63,455,095	10q21	*ARID5B*	2	0.085	0.17	-	-
rs3781913	11	72,051,144	11q13	*PDE2A-ARAP1*	9	0.0032	0.029	GI_30157198-S	*STARD10*
rs2841277	14	104,462,050	14q32	*PLD4*	19	0.077	1	-	-
rs2847297	18	12,787,694	18p11	*PTPN2*	7	0.079	0.56	-	-

[a]Based on forward strand and NCBI Build 36.3.

[b]No. cis-probes located ± 300 kbp of the landmark SNP and previously measured in lymphoblastoid B cell lines obtained from HapMap Phase II East Asian populations (GSE6536)[1].

[c]The smallest *P*-value obtained from correlation analysis between SNP genotypes and expression levels of cis-probes.

[d]The smallest *P*-value obtained from correlation analysis after the application of Bonferroni correction based on the number of cis-probes.

[e]Cis-eQTL probes and corresponding genes which demonstrated significant associations after Bonferroni correction (corrected $P < 0.05$).

Supplementary Table 5. Associations of the identified loci with SLE and Graves' disease.

rsID[a]	Chr	Position (bp)	Cyto-band	Gene(s)	Allele 1/2	Associations with SLE					Associations with Graves' disease				
						Allele 1 Freq.		OR (95%CI)[b]	*P*	Power[c]	Allele 1 Freq.		OR (95%CI)[b]	*P*	Power[c]
						Cases (*n* = 891)	Control (*n* = 3,384)				Cases (*n* = 1,783)	Control (*n* = 3,384)			
rs11900673	2	62,306,165	2p15	*B3GNT2*	T/C	0.30	0.29	1.07 (0.96-1.20)	0.23	5.4%	0.32	0.29	1.17 (1.08-1.28)	3.5×10^{-4}	77.0%
rs2867461	4	79,732,239	4q21	*ANXA3*	A/G	0.48	0.44	1.17 (1.05-1.29)	0.0040	56.8%	0.47	0.44	1.12 (1.03-1.22)	0.0057	48.1%
rs657075	5	131,458,017	5q31	*CSF2*	A/G	0.37	0.36	1.05 (0.95-1.17)	0.33	3.0%	0.38	0.36	1.08 (0.99-1.18)	0.067	16.0%
rs12529514	6	14,204,637	6p23	*CD83*	C/T	0.16	0.15	1.11 (0.97-1.28)	0.13	9.1%	0.15	0.15	1.00 (0.89-1.12)	0.94	< 0.1%
rs10821944	10	63,455,095	10q21	*ARID5B*	G/T	0.39	0.36	1.11 (1.00-1.24)	0.052	19.2%	0.40	0.36	1.17 (1.08-1.27)	2.9×10^{-4}	82.0%
rs2233434	6	44,340,898	6p21.1	*NFKBIE*	G/A	0.22	0.22	1.04 (0.92-1.18)	0.51	1.6%	0.21	0.22	0.99 (0.90-1.09)	0.81	< 0.1%
rs3781913	11	72,051,144	11q13	*PDE2A-ARAP1*	T/G	0.70	0.69	1.04 (0.93-1.17)	0.48	1.9%	0.69	0.69	0.96 (0.88-1.05)	0.42	3.2%
rs2841277	14	104,462,050	14q32	*PLD4*	T/C	0.72	0.68	1.18 (1.05-1.32)	0.0057	52.0%	0.69	0.68	1.05 (0.96-1.15)	0.27	4.7%
rs2847297	18	12,787,694	18p11	*PTPN2*	G/A	0.36	0.35	1.06 (0.95-1.18)	0.33	4.3%	0.37	0.35	1.08 (0.99-1.17)	0.092	16.2%

[a]SNPs that satisfied $P < 5.0 \times 10^{-8}$ with rheumatoid arthritis in the combined study are indicated based on forward strand and NCBI Build 36.3.

[b]Odds ratio of allele 1.

[c]Estimated based on $\alpha = 0.05/9 = 0.0056$, number of the subjects in the cohort of SLE or Graves' disease, allele frequency in the controls, and odds ratio of the SNP obtained for SLE or Graves' disease, using Genetic Power Calculator (http://pngu.mgh.harvard.edu/~purcell/gpc/).

SLE, systemic lupus erythematosus; OR, odds ratio; 95%CI, 95% confidence interval.

Supplementary Table 6. Associations in the previously reported loci associated with rheumatoid arthritis.

rsID[a]	Chr	Position (bp)	Cyto-band	Gene(s)	Allele 1/2	GWAS meta-analysis in Japaneses				GWAS meta-analysis in Europeans[c]				Associations in[d]	
						Allele 1 Freq.		OR (95%CI)[b]	*P*	Allele 1 Freq.		OR (95%CI)[b]	*P*	Japanese	Europeans
						RA	Control			RA	Control				
rs3890745	1	2,585,786	1p36	*TNFRSF14*	T/C	0.54	0.51	1.11 (1.06-1.17)	6.8E-05	0.71	0.68	1.12 (1.06-1.18)	5.6E-06	+	+
rs766449	1	17,420,158	1p36	*PADI4*	T/C	0.44	0.40	1.17 (1.11-1.24)	4.6E-08	0.38	0.37	1.09 (1.03-1.15)	0.0022	++	+
rs2476601	1	114,089,610	1p13	*PTPN22*	A/G	0.00	0.00	NA		0.17	0.10	1.94 (1.80-2.09)	6.2E-71		++
rs11586238	1	116,975,180	1p13	*CD2-CD58*	G/C	0.042	0.042	0.94 (0.82-1.07)	0.35	0.26	0.23	1.13 (1.07-1.19)	1.5E-05		+
rs10430455	1	154,516,311	1q23	*FCRL3*	T/A	0.41	0.38	1.12 (1.06-1.18)	7.2E-05	0.47	0.45	1.08 (1.03-1.13)	9.0E-04	+	+
rs12746613	1	158,280,097	1q23	*FCGR2A*	T/C	0.00	0.00	NA		0.13	0.12	1.13 (1.05-1.21)	5.7E-04		+
rs6682654	1	159,075,627	1q23	*CD244*	G/A	0.63	0.62	1.05 (0.99-1.10)	0.087	0.44	0.43	1.02 (0.98-1.06)	0.37		
rs10919563	1	195,432,099	1q31	*PTPRC*	G/A	0.77	0.77	0.99 (0.93-1.05)	0.67	0.89	0.87	1.14 (1.06-1.22)	3.3E-04		+
rs13031237	2	61,047,780	2p16	*REL*	T/G	0.033	0.037	0.97 (0.84-1.13)	0.71	0.39	0.36	1.13 (1.08-1.19)	1.3E-06		+
rs11900673	2	62,364,312	2p15	*B3GNT2*	T/C	0.31	0.28	1.15 (1.08-1.21)	3.5E-06	0.13	0.13	1.05 (0.98-1.13)	0.17	+	
rs934734	2	65,507,237	2p14	*SPRED2*	G/A	0.19	0.16	1.19 (1.12-1.27)	3.2E-07	0.52	0.49	1.13 (1.08-1.19)	5.5E-07	+	+
rs11676922	2	100,265,458	2q11	*AFF3*	T/A	0.51	0.49	1.10 (1.04-1.16)	5.0E-04	0.49	0.46	1.12 (1.07-1.17)	1.1E-06	+	+
rs7574865	2	191,790,139	2q32	*STAT4*	T/G	0.36	0.33	1.16 (1.09-1.22)	8.9E-07	0.25	0.22	1.16 (1.09-1.23)	4.9E-07	+	+
rs1980422	2	204,435,902	2q33	*CD28*	C/T	0.063	0.068	0.92 (0.64-1.34)	0.67	0.26	0.24	1.12 (1.06-1.18)	7.4E-05		+
rs3087243	2	204,564,425	2q33	*CTLA4*	G/A	0.75	0.73	1.10 (1.04-1.16)	0.0023	0.61	0.56	1.15 (1.10-1.20)	2.2E-08	+	++
rs13315591	3	58,531,881	3p14	*PXK*	C/T	0.00	0.00	NA		0.10	0.086	1.29 (1.17-1.43)	6.3E-07		+
rs874040	4	25,784,466	4p15	*RBPJ*	C/G	0.00	0.00	NA		0.33	0.30	1.14 (1.08-1.20)	3.3E-07		+
rs2867461	4	79,870,394	4q21	*ANXA3*	A/G	0.46	0.44	1.13 (1.08-1.19)	4.7E-06	0.37	0.37	0.98 (0.92-1.04)	0.52	+	
rs6822844	4	123,867,026	4q27	*IL2-IL21*	G/T	1.00	1.00	NA		0.84	0.82	1.11 (1.04-1.18)	8.3E-04		+
rs6859219	5	55,474,337	5q11	*ANKRD55-IL6ST*	C/A	0.98	0.97	1.26 (1.00-1.59)	0.044	0.82	0.79	1.28 (1.18-1.39)	5.1E-09		++
rs26232	5	102,624,619	5q21	*C5orf30*	C/T	0.73	0.72	1.01 (0.95-1.07)	0.75	0.71	0.68	1.14 (1.08-1.19)	7.3E-07		+
rs657075	5	131,458,017	5q31	*CSF2*	A/G	0.38	0.36	1.12 (1.06-1.18)	3.2E-05	0.10	0.10	1.04 (0.95-1.13)	0.37	+	
rs12529514	6	14,204,637	6p23	*CD83*	C/T	0.16	0.14	1.19 (1.10-1.27)	6.8E-06	0.055	0.053	1.11 (0.99-1.24)	0.074	+	
rs2157337	6	32,609,122	6p21.3	*HLA-DRB1*	C/T	0.59	0.44	1.99 (1.88-2.11)	2.6E-118	0.69	0.46	2.50 (2.39-2.62)	< 10E-300	++	++
rs2233434	6	44,340,898	6p21.1	*NFKBIE*	G/A	0.24	0.21	1.23 (1.16-1.31)	9.2E-11	0.059	0.040	1.57 (1.11-2.21)	0.0099	++	
rs548234	6	106,674,727	6q21	*PRDM1*	C/T	0.34	0.33	1.02 (0.97-1.08)	0.41	0.34	0.33	1.10 (1.05-1.16)	1.3E-04		+
rs5029937	6	138,236,844	6q23	*TNFAIP3*	T/G	0.089	0.068	1.33 (1.21-1.45)	3.9E-09	0.046	0.036	1.40 (1.24-1.59)	1.4E-07	++	+
rs394581	6	159,452,930	6q25	*TAGAP*	T/C	0.98	0.97	1.23 (1.04-1.46)	0.022	0.73	0.70	1.10 (1.04-1.16)	7.7E-04		+
rs3093023	6	167,504,701	6q27	*CCR6*	A/G	0.52	0.46	1.27 (1.20-1.34)	2.1E-17	0.47	0.43	1.13 (1.08-1.19)	5.7E-07	++	+
rs10488631	7	128,188,134	7q32	*IRF5*[e]	C/T	0.00	0.00	NA		0.13	0.11	1.19 (1.10-1.28)	4.3E-06	+	+
rs13225818	7	128,329,965			T/C	0.88	0.86	1.23 (1.14-1.33)	4.0E-07	0.83	0.85	0.93 (0.87-0.99)	0.022		
rs2736340	8	11,381,382	8p23	*BLK*	T/C	0.72	0.69	1.12 (1.06-1.18)	1.2E-04	0.27	0.25	1.12 (1.06-1.18)	2.2E-05	+	+
rs951005	9	34,733,681	9p13	*CCL21*	A/G	0.98	0.98	1.08 (0.88-1.32)	0.45	0.86	0.84	1.19 (1.11-1.28)	9.1E-07		+
rs3761847	9	120,769,793	9q33	*TRAF1-C5*	G/A	0.53	0.52	1.06 (1.01-1.12)	0.025	0.46	0.43	1.13 (1.08-1.18)	3.7E-07		+
rs706778	10	6,138,955	10p15	*IL2RA*	T/C	0.57	0.56	1.02 (0.96-1.07)	0.55	0.44	0.41	1.14 (1.09-1.20)	1.4E-07		+
rs4750316	10	6,433,266	10p15	*PRKCQ*	G/C	0.88	0.88	1.00 (0.92-1.08)	0.92	0.83	0.81	1.15 (1.09-1.22)	3.2E-06		+
rs10821944	10	63,455,095	10q21	*ARID5B*	G/T	0.39	0.36	1.17 (1.11-1.23)	1.0E-08	0.29	0.26	1.11 (1.05-1.17)	1.9E-04	++	+
rs540386	11	36,481,869	11p12	*TRAF6*	C/T	0.97	0.97	1.09 (0.88-1.35)	0.45	0.87	0.86	1.14 (1.06-1.22)	3.8E-04		+
rs3781913	11	72,051,144	11q13	*PDE2A-ARAP1*	T/G	0.71	0.69	1.11 (1.05-1.17)	3.2E-04	0.45	0.43	1.04 (0.99-1.09)	0.13	+	
rs10892279	11	118,116,991	11q23	*DDX6*	G/A	0.81	0.80	1.08 (1.01-1.15)	0.030	0.82	0.80	1.15 (1.09-1.22)	5.8E-06		+
rs1678542	12	56,254,982	12q13	*KIF5A-PIP4K2C*	C/G	0.21	0.20	1.05 (0.98-1.11)	0.18	0.64	0.62	1.10 (1.04-1.15)	2.3E-04		+
rs2841277	14	104,462,050	14q32	*PLD4*	T/C	0.72	0.69	1.11 (1.05-1.18)	2.8E-04	0.47	0.46	1.02 (0.96-1.09)	0.54	+	
rs2847297	18	12,787,694	18p11	*PTPN2*	G/A	0.37	0.33	1.16 (1.11-1.23)	3.5E-08	0.36	0.34	1.10 (1.05-1.15)	9.2E-05	++	+
rs4810485	20	44,181,354	20q13	*CD40*	G/T	0.63	0.61	1.08 (1.02-1.14)	0.0054	0.78	0.75	1.18 (1.11-1.25)	5.7E-09		++
rs2075876	21	44,533,581	21q22	*AIRE*	A/G	0.38	0.35	1.14 (1.08-1.20)	2.8E-06	0.12	0.12	1.00 (0.93-1.08)	0.94	+	
rs3218253	22	35,869,310	22q12	*IL2RB*	A/G	0.072	0.071	0.99 (0.90-1.10)	0.88	0.28	0.26	1.09 (1.03-1.15)	0.0027		+

[a]Based on forward strand and NCBI Build 36.3. The risk allele for rheumatoid arthritis in the previously reported studies[2-19] was denoted as allele 1.

[b]Odds ratio of allele 1.

[c]Associations in the previous meta-analysis in the European populations are referenced[15].

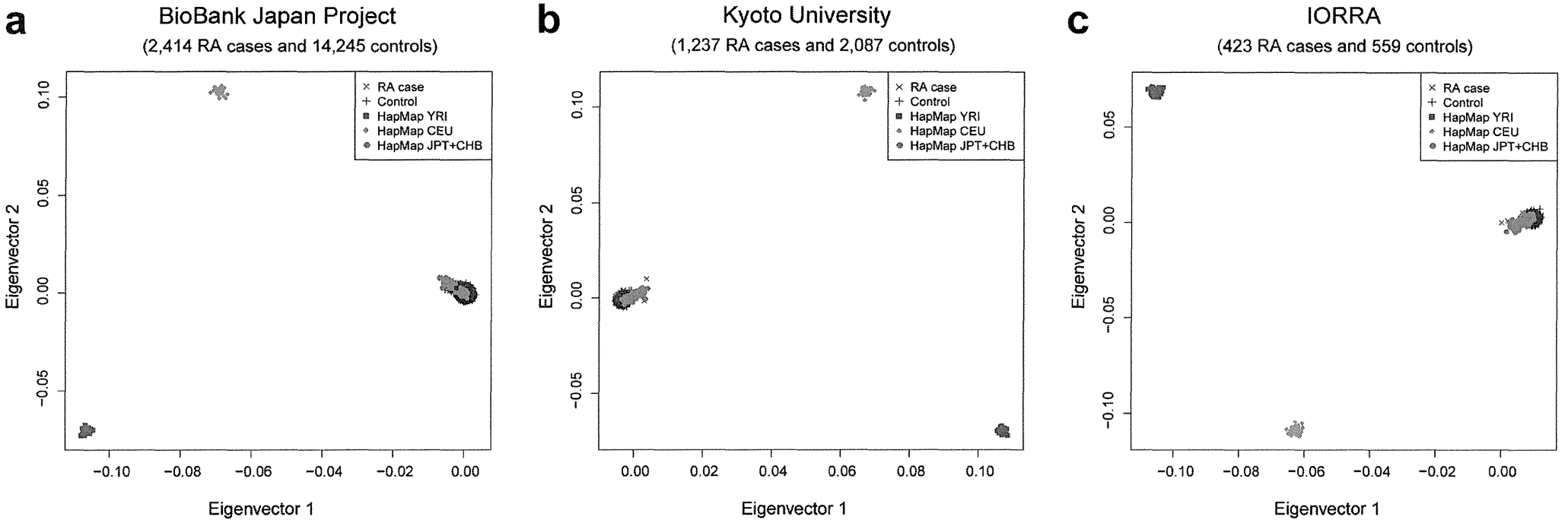
[d]*P*-value that satisfied genome-wide significance threshold ($P < 5.0 \times 10^{-8}$) and false discovery rate (FDR) < 0.05 ($5.0 \times 10^{-8} \leq P < 0.0030$) are indicated as "++" and "+", respectively.

[e]In the *IRF5* locus, different causal variants were reported for the Japanese and European populations[15,20].

GWAS, genome-wide association study; RA, rheumatoid arthritis; OR, odds ratio; 95%CI, 95% confidence interval; NA, not available.

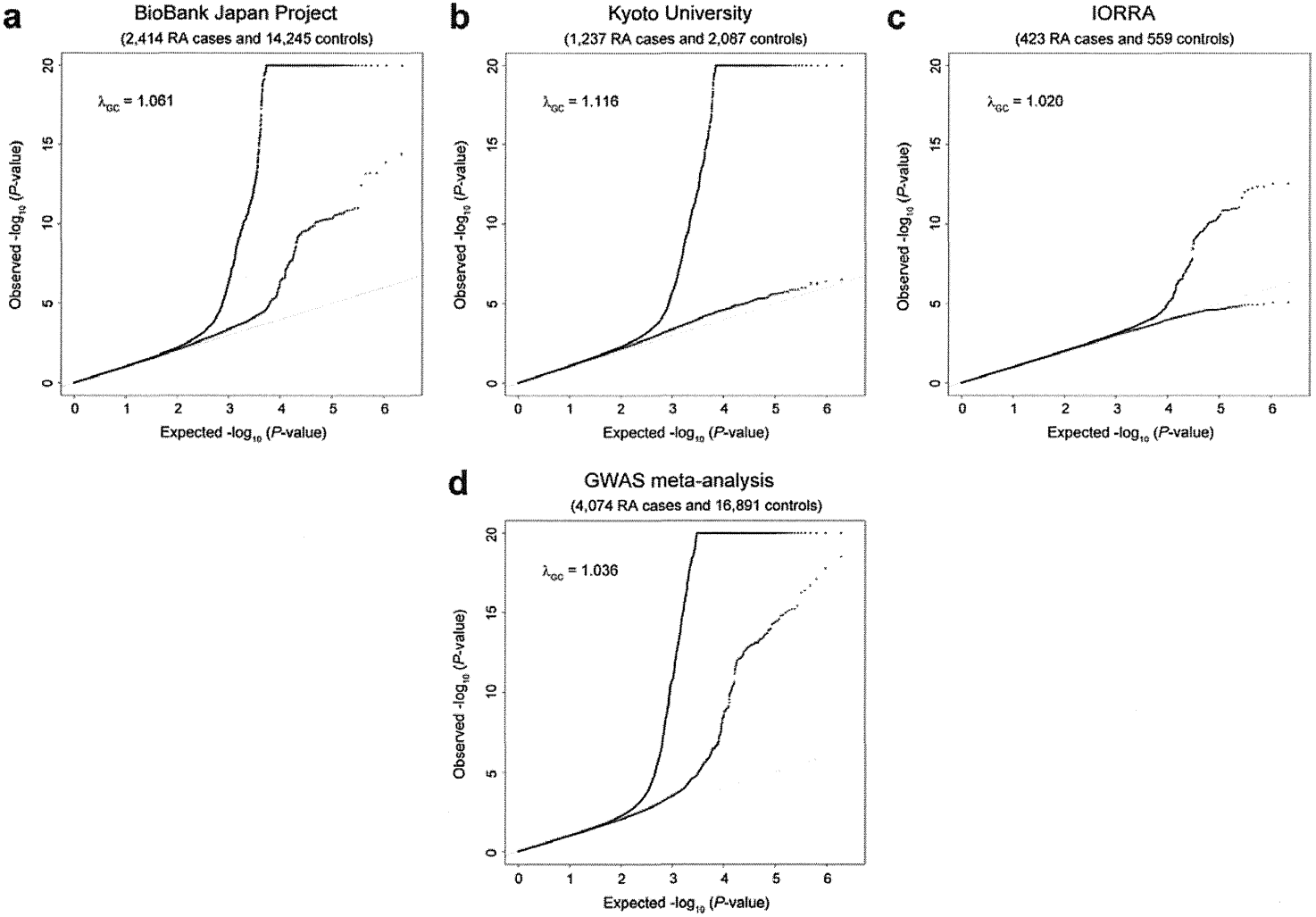
Supplementary Figure 1. Distribution of subjects in the results of principal component analysis (PCA).

Two dimensional display of subjects finally included in the GWAS conducted by **(a)** BioBank Japan Project, **(b)** Kyoto university, and **(c)** IORRA representing the results of PCA[21] performed along with HapMap European (CEU), African (YRI), Japanese (JPT), and Han Chinese (CHB) individuals (Phase II, release 24)[22]. The eigenvectors clearly separated the subjects into three clusters (YRI, CEU, and JPT + CHB clusters), and the distribution of the subjects in the GWAS was concordant with the JPT + CHB cluster as previously anticipated in the Japanese population[23].



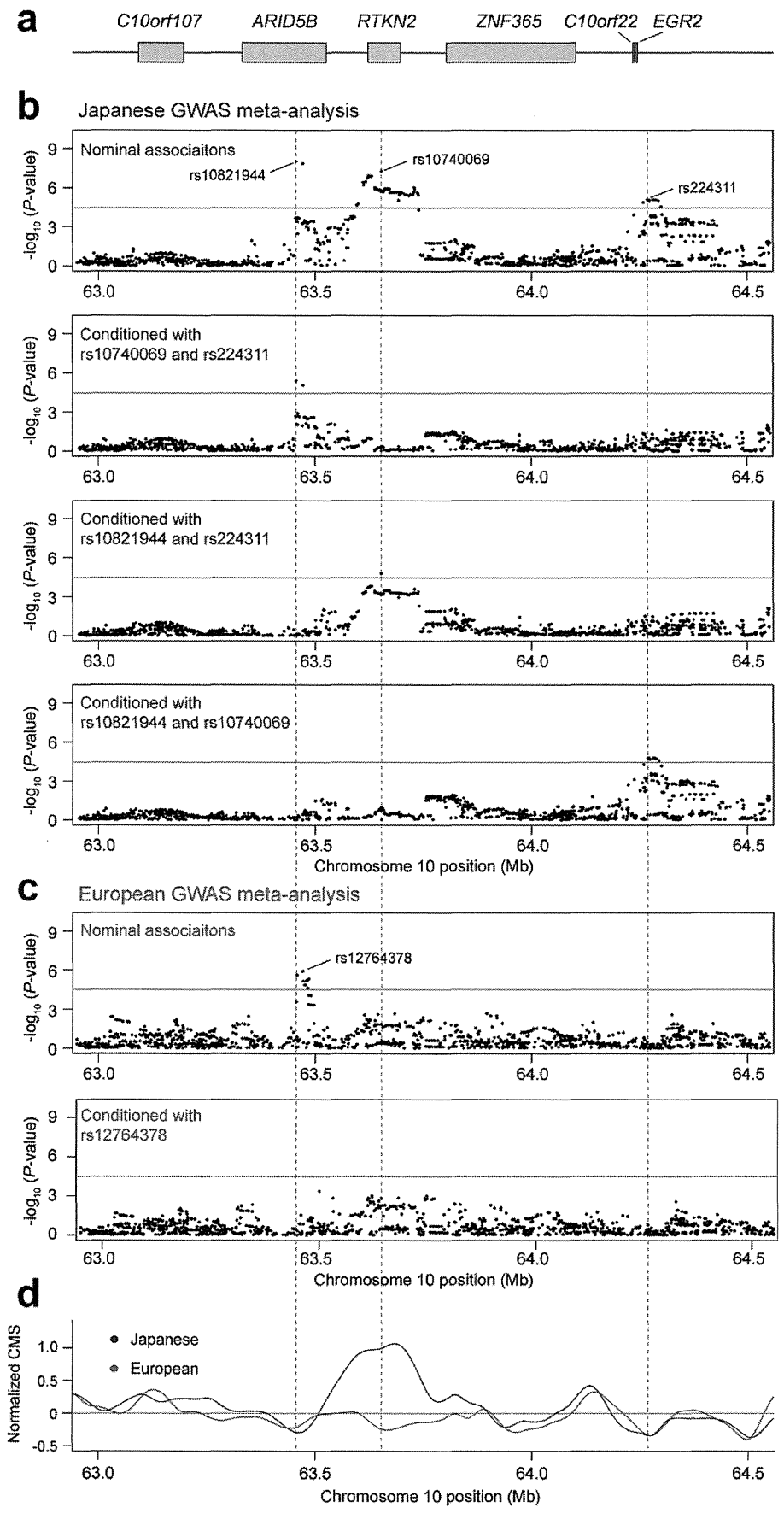
Supplementary Figure 2. Quantile-Quantile plots of *P*-values in the GWAS meta-analysis.

Quantile-Quantile (QQ) plots of the *P*-values in the GWAS conducted by **(a)** BioBank Japan Project, **(b)** Kyoto University, and **(c)** IORRA, and **(d)** the present GWAS meta-analysis. The QQ-plot of the *P*-values of all SNPs that passed the quality control criteria is indicated in black. The QQ-plot of the *P*-values after the removal of SNPs included in the MHC region is presented in blue. The horizontal axis represents the expected $-\log_{10}$ (*P*-values). The vertical axis indicates the observed $-\log_{10}$ (*P*-values) after the application of genomic control correction[24,25] with inflation factor, λ_{GC}, which is displayed in each of the plots. The gray line represents $y = x$, which corresponds to the null hypothesis. The SNPs for which the *P*-value were smaller than 1.0×10^{-20} are indicated at the upper limit of the plot.



Supplementary Figure 3. Regional plots of the SNPs in the *ARID5B* locus at 10q21.

(a) The RefSeq genes in the locus. Associations of the SNPs before and after the condition with the landmark SNP(s) **(b)** in the present Japanese GWAS meta-analysis and **(c)** the previous European GWAS meta-analysis[15]. Dots represent $-\log_{10}$ (*P*-values) of the SNPs in the GWAS meta-analysis. The gray horizontal line represents the region-wide threshold of $P = 0.05/1420 = 3.5 \times 10^{-5}$ (Bonferroni correction on the number of the assessed SNPs located between 63.0 Mbps and 64.5 Mbps). The red dotted lines represent the correspondence of the chromosomal positions of the landmark SNPs in **b** and **c**. In Japanese, three peaks of associations on, or near, *ARID5B*, *RTKN2*, and *EGR2* were observed ($P = 1.0 \times 10^{-8}$ at rs10821944, $P = 5.7 \times 10^{-8}$ at rs10740069, and $P = 8.5 \times 10^{-6}$ at rs224311, respectively; the first panel of **b**). These three variants indicated independent associations with each of the other SNPs (conditional $P = 4.3 \times 10^{-6}$, 1.7×10^{-5}, and 1.8×10^{-5}, respectively; the second to fourth panels of **b**). In contrast, there was only one peak at *ARID5B* observed in Europeans ($P = 1.2 \times 10^{-6}$ at rs12764378; the first panel of **c**) and no further association was observed in the conditional analysis with rs12764378 (the smallest conditional $P = 2.2 \times 10^{-4}$; the second panel of **c**), suggesting that the numbers of independent associations may be different in the locus between the two populations. **(d)** Spline curves of population-specific normalized composite of multiple signals (CMS), an index of positive selection[26]. Since the genetic locus with causal variants is likely to undergo natural selection, we evaluated population-specific selective signals of the locus using CMS calculated in HapMap Phase II East Asian and Caucasian individuals, respectively. Significance of natural selection pressure was assessed by comparing the mean value of population-specific CMS for the SNPs located ± 100 kbp of the landmark SNP with those from the SNPs located ± 100 kbp of randomly selected whole genome SNPs by a permutation procedure (× 20,000 iterations). Results suggested a significant positive selection pressure in Japanese near rs10740069 (permutation $P = 0.0092$), although no selective signal was implicated in Europeans ($\alpha = 0.05$), that was analogous to the regional associations on RA. This observation might suggest the existence of causal variant(s) in the locus, which may have specifically evolved in the Japanese population through a population-specific pressure of natural selection.


a
C10orf107
ARID5B
RTKN2
ZNF365
C10orf22
EGR2
b
Japanese GWAS meta-analysis
Nominal associaitons
rs10821944
rs10740069
rs224311
Conditioned with rs10740069 and rs224311
Conditioned with rs10821944 and rs224311
Conditioned with rs10821944 and rs10740069
-log10 (P-value)
Chromosome 10 position (Mb)
c
European GWAS meta-analysis
Nominal associaitons
rs12764378
Conditioned with rs12764378
d
Normalized CMS
Japanese
European

Supplementary Note

I. Descriptions of the participating cohorts

1. Rheumatoid arthritis (RA) case-control cohorts.

In the present study, we included a total of 9,351 RA cases and 38,575 controls not affected with autoimmune diseases in the Japanese population. The study consisted of three genome-wide association studies (GWAS; 4,074 RA cases and 16,891 controls) and two independent replication studies (5,277 RA cases and 21,684 controls). The GWAS were conducted by the BioBank Japan Project (2,414 RA cases and 14,245 controls)[16,27], Kyoto University (1,237 RA cases and 2,087 controls)[19], and the Institute of Rheumatology Tokyo Women's Medical University (IORRA: Institute of Rheumatology RA cohort; 423 RA cases and 559 controls), respectively. The replication study 1 consisted of 3,830 RA cases from the BioBank Japan Project[27] (*n* = 1,172), Center for Genomic Medicine at RIKEN (*n* = 1,014), and IORRA (*n* = 1,644)[28]. Control subjects (*n* = 17,920) were recruited from the BioBank Japan project[27]. The replication study 2 consisted of 1,447 RA cases and 3,764 controls from Kyoto University. All the RA cases satisfied the revised criteria of the American Rheumatism Association for rheumatoid arthritis[29]. All participants in each cohort provided written informed consent for participation in the study as approved by the ethical committees of each of the institutional review boards. Characteristics of the subjects and the genotyping platforms are provided in **Supplementary Table 1 and 2**. Detailed descriptions of the cohorts are described below.

1.1 The BioBank Japan Project.

The BioBank Japan Project (http://biobankjp.org) started at the Institute of Medical Science, the University of Tokyo in 2003. To date, the BioBank Japan Project has collected up to 300,000 individuals with disease cases consisting of 47 various diseases[27]. These subjects were recruited from 12 medical institutes in Japan including, Osaka Medical Center for Cancer and Cardiovascular Diseases, the Cancer Institute Hospital of Japanese Foundation for Cancer Research, Juntendo University, Tokyo Metropolitan Geriatric Hospital, Nippon Medical School, Nihon University School of Medicine, Iwate Medical University, Tokushukai Hospitals, Shiga University of Medical Science, Fukujuji Hospital, National Hospital Organization Osaka National Hospital, and Iizuka Hospital. Subjects who were determined not to be of Japanese origin by self-report, by principal component analyses, or by our previous studies[16,23] were excluded from the current analyses.

1.2 Kyoto University.

Kyoto University collected DNA samples from 5,303 patients with connective tissue diseases including RA (*n* =

4,195)[29], systemic lupus erythematosus (n = 440), and systemic sclerosis (n = 191) as well as DNA samples of more than 10,000 healthy people and 4,000 patients with other diseases. RA patients were recruited at Kyoto University Hospital, Dohgo Spa Hospital, Sagamihara National Hospital, Niigata Rheumatic Center, and Saiseikai Takaoka Hospital. All subjects are Japanese by self-report. Possible overlapping samples with subjects in the BioBank Japan Project and IORRA cohorts were excluded from genome-scan and replication study.

1.3 Institute of Rheumatology Tokyo Women's Medical University (IORRA).

IORRA cohort is a long-term prospective observational cohort of RA patients at the Institute of Rheumatology, Tokyo Women's Medical University established in 2000[28]. For each patient, a survey composed of three domains (background variables, physician's evaluation, and laboratory test data) is conducted biannually to create a database. Of these, DNA samples were collected from 2,068 of these patients. Control samples for the IORRA case-control study are obtained from unrelated healthy Japanese adults who were recruited in Tokyo and Nagoya, Japan[30].

2. Systemic lupus erythematosus (SLE) case-control cohort.

We included 891 SLE cases and 3,384 matched controls, who were enrolled in the previously conducted GWAS in a Japanese populations[31]. SLE cases were collected from several medical institutes in Japan under the support of the Autoimmune Disease study group of Research in intractable Diseases (ADRD), Japanese Ministry of Health, Labor and Welfare. SLE cases met the revised American College of Rheumatology (ACR) criteria for SLE[32]. A portion of the control subjects overlapped with those used in the present GWAS on RA with 905 individuals coming from Kyoto University, and 2,479 individuals coming from the replication study 1. All subjects were of Japanese ancestry and provided written informed consent.

3. Greave's disease (GD) case-control cohort.

We included 1,783 GD cases and 3,384 controls (the same controls from the SLE case-control cohort). The GD cases have been included in our previous study[16]. Diagnoses of individuals with GD were established on the basis of clinical findings and results of routine examinations for circulating thyroid hormone and thyroid-stimulating hormone concentrations, thyroid-stimulating hormone receptors, ultrasonography, $^{[99m]}TCO4^-$ (or $[^{123}I]$) uptake, and thyroid scintigraphy. All subjects were of Japanese origin and provided written informed consent.

II. Genes in the newly identified rheumatoid arthritis (RA) susceptibility loci.

Genes which are located nearest to the landmark SNPs in each of the newly identified RA susceptibility loci are highlighted here. Nevertheless, additional genes neighboring the loci could also be candidates of causal origins. Further investigations into the functionality of these genes are warranted. It should be noted that cis-expression quantitative trait loci (cis-eQTL) analysis of landmark SNPs using lymphoblastoid B cell lines[1] suggested additional genes as possible candidates, such as *P4HA4* at 5q31, *AARS2* at 6p21.1, and *STARD10* at 11q13 (**Supplementary Table 4**), although relatively small sample size included in the eQTL study (n = 90) and lack of statistical power would provide limited conclusions. Among the landmark SNPs of the loci and the SNPs in linkage disequilibrium (LD) with them (r^2 > 0.8), rs2233434 at 6p21.1 and four SNPs in LD with rs2841277 at 14q32 had non-synonymous substitutions in *NFKBIE* (606A/G in exon 1) and *AHNAK2* (the strongest LD at rs9672139, r^2 = 0.97, 13726A/C in exon 7), respectively.

***B3GNT2* at 2p15.** *B3GNT2* (UDP-GlcNAc:betaGal beta-1,3-N-acetylglucosaminyltransferase 2) is a major synthase for polylactosamine, which has an important role for the regulation of lymphocyte activitiy[33]. The *B3GNT2* locus was reported to be associated with ankylosing spondylitis, an inflammatory arthritis in spine[34].

***ANXA3* at 4q21.** *ANXA3* (annexin A3) belongs to the annexin family, which encodes proteins related to calcium-dependent binding to phospholipid[35]. Annexin A3 is highly expressed in neutrophils and involved in the aggregation of cytosolic granules.

***CSF2* at 5q31.** *CSF2* (colony stimulating factor 2, also known as *GM-CSF*) regulates myeloid cell production and differentiation, and has been recognized as a promising therapeutic target of RA[36]. It should be noted that both the present study in Japanese and previous study in Europeans[15] observed suggestive associations (P < 5.0×10^{-4}) at 17q12, where another well-known myeloid growth factor of *CSF3* (also known as *G-CSF*) is located.

***CD83* at 6p23.** *CD83* (cluster of differentiation, 83 molecule) is preferentially expressed on dendritic cells and is involved in antigen-presentation and lymphocyte activation[37]. To note, CD83-deficient mice lack T-cell development.

***NFKBIE* at 6p21.1.** *NFKBIE* (nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, epsilon) encodes IκB epsilon (IκBε), which binds to components of NF-κB and inhibits the nuclear translocation of NF-κB[38].

***ARID5B* at 10q21.** *ARID5B* (AT rich interactive domain 5B, MRF1-like) is a transcription factor that mediates embryogenesis, and is known as a risk locus for acute lymphoblastic leukemia[39].

***PDE2A* and *ARAP1* at 11q13.** *PDE2A* (phosphodiesterase 2A, cGMP-stimulated) encodes an enzyme that