Genome-wide association study of asthma identifies RAD50-IL13 and HLA-DR/DQ regions

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Background: Asthma is a heterogeneous disease that is caused by the interaction of genetic susceptibility with environmental influences. Genome-wide association studies (GWASs) represent a powerful approach to investigate the association of DNA variants with disease susceptibility. To date, few GWASs for asthma have been reported.

Objectives: A GWAS was performed on a population of patients with severe or difficult-to-treat asthma to identify genes that are involved in the pathogenesis of asthma.

Methods: A total of 292,443 single nucleotide polymorphisms (SNPs) were tested for association with asthma in 473 The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) cases and 1892 Illumina general population controls. Asthma-related quantitative traits (total serum IgE, FEV_1, forced vital capacity, and FEV_1/forced vital capacity) were also tested in identified candidate regions in 473 TENOR cases and 363 phenotyped controls without a history of asthma to analyze GWAS results further. Imputation was performed in identified candidate regions for analysis with denser SNP coverage.

Results: Multiple SNPs in the RAD50-IL13 region on chromosome 5q31.1 were associated with asthma: rs2244012 in intron 2 of *RAD50* ($P = 3.04E-07$). The HLA-DR/DQ region on chromosome 6p21.3 was also associated with asthma: rs1063355 in the 3′ untranslated region of *HLA-DQB1* ($P = 9.55E-06$). Imputation identified several significant SNPs in the T_H2 locus control region 3′ of *RAD50*. Imputation also identified a more significant SNP, rs3998159 ($P = 1.45E-06$), between *HLA-DQB1* and *HLA-DQA2*.

Conclusion: This GWAS confirmed the important role of T_H2 cytokine and antigen presentation genes in asthma at a genome-wide level and the importance of additional investigation of these 2 regions to delineate their structural complexity and biologic function in the development of asthma. (J Allergy Clin Immunol 2010;125:328-35.)

Key words: *Asthma, GWAS, RAD50, IL13, HLA-DQB1, TENOR*

Asthma is a complex disease that is caused by the interaction of genetic susceptibility with environmental influences. Genome-wide linkage studies, candidate-gene association studies, and genome-wide association studies (GWASs) represent 3 major approaches to investigate the association between genetic variants and disease development.

Genome-wide linkage studies have consistently identified regions linked to asthma or asthma-related traits on chromosome 2q, 5q, 6p, 12q, and 13q.[1] The most highly replicated regions with obvious candidate genes are chromosome 5q31-33 (including *IL5*, *IL13*, *IL4*, *CD14*, and adrenergic β-2-receptor) and 6p21 (including lymphotoxin-α [or *TNFB*], *TNF*, major MHC-II, *HLA-DQB1*, and *HLA-DRB1*).[2] In addition, a recent meta-analysis of genome-wide linkage studies of asthma, bronchial hyperresponsiveness, positive allergen skin prick test, and total IgE identified overlapping regions for multiple phenotypes on chromosomes 5q and 6p as well as 3p and 7p.[3] Unfortunately, genome-wide linkage studies can only identify genes with relative strong effects in broad regions that include many genes. Positional cloning studies have identified 6 genes for asthma: a disintegrin and metalloprotease domain 33 on chromosome 20p13,[4] dipeptidyl-peptidase 10 on 2q14.1,[5] PHD finger protein 11 on 13q14.11,[6] neuropeptide S receptor 1 (or *GPRA*) on 7p14.3,[7] MHC-I, G (*HLA-G*) on 6p21.3,[8] and cytoplasmic FMR1 interacting protein 2 on 5q33.3.[9]

Candidate-gene association studies have identified more than 100 genes for asthma and asthma-related traits.[2,10,11] Although candidate-gene association studies have identified many genes, only a few have been replicated extensively. Thus, only 14 genes including genes on 5q and 6p (adrenergic β-2-receptor, IL-4 receptor, *HLA-DRB1*, *IL13*, *CD14*, *TNF*, membrane-spanning 4-domains, subfamily A, member 2 [or *FCER1B*], *IL4*, a disintegrin and metalloprotease domain 33, signal transducer and activator of transcription 6, IL4 induced, *IL10*, *HLA-DQB1*, glutathione S-transferase π 1, and lymphotoxin-α) have been replicated in more than 20 independent studies.[10] Even for highly replicated genes, replication might be a result of winner's bias and/or loose replication standard (gene as a unit and related phenotypes).

A GWAS is a hypothesis-free approach able to identify novel genes with mild/moderate effects and thus has become the best approach for studying association between genes and common disease phenotypes. To date, only 4 GWASs have been performed for asthma and asthma-related traits.[12] The first GWAS of childhood asthma identified ORM1-like 3 on chromosome 17q12.[13] The second GWAS of serum YKL-40 levels identified chitinase 3-like 1 on 1q32.[14] The third GWAS was for a related trait, total

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The clinical TENOR study was supported by Genentech, Inc, and Novartis Pharmaceuticals Corp, and this genetic study was funded by NIH HL76285 and HL87665.

Disclosure of potential conflict of interest: D. A. Meyers has received research support from the National Institutes of Health. S. P. Peters has consulted for Genentech and has received research support from Genentech and the National Institutes of Health/National Heart, Lung, and Blood Institute. E. R. Bleecker is a member of Genentech's TENOR Steering Committee and has received research support (but no personal income) from Genentech and the National Institutes of Health. T. Haselkorn has consulted for Genentech. The rest of the authors have declared that they have no conflict of interest.

Received for publication August 6, 2009; revised October 1, 2009; accepted for publication November 13, 2009.

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0091-6749/$36.00

doi:10.1016/j.jaci.2009.11.018

Abbreviations used
FVC: Forced vital capacity
GC: Genomic control
GWAS: Genome-wide association study
IBS: Identity-by-state
LCR: Locus control region
LD: Linkage disequilibrium
MAF: Minor allele frequency
QC: Quality control
SNP: Single nucleotide polymorphism
TENOR: The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens

serum IgE levels, and the most significant single nucleotide polymorphisms (SNPs) are in the Fc fragment of IgE, high-affinity I, receptor for α polypeptide gene (*FCER1A*) on chromosome 1q23, and the second highest region observed was *RAD50* on 5q31.[15] The fourth GWAS of childhood asthma indicated phosphodiesterase 4D, cyclic adenosine monophosphate–specific (phosphodiesterase E3 dunce homolog, *Drosophila*) (*PDE4D*) on chromosome 5q12.[16]

In this study, we performed a GWAS of asthma in The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) population of severe or difficult to treat asthmatics to search for novel genes and to confirm previously identified genes involved in asthma. The purpose of the TENOR study was to investigate the natural history of asthma in a large cohort of well characterized patients with severe or difficult to treat asthma; no treatment intervention was involved, and patients continued to be treated by their asthma specialists.[17-19]

METHODS

Study subjects

The TENOR study was a multicenter observational and longitudinal cohort study of 4756 patients with asthma described as "severe or difficult-to-treat" by their physicians, sponsored by Genentech and Novartis.[17] Subjects were included if they had physician-characterized difficult-to-treat asthma and met additional criteria based on frequency of urgent care visits and/or the use of multiple controller medications. The clinical sites from the original TENOR study were contacted and invited to participate in this study. Sites that agreed were mailed Oragene DNA saliva collection kits (DNA Genotek, Inc, Ontario, Canada), labeled with the TENOR participant identification number. Sites then mailed the kits to participating individuals, who sent their collected samples to the Center for Human Genomics at Wake Forest University School of Medicine. This process was required to maintain anonymity between investigators at Wake Forest University and the study participants. Unfortunately, the TENOR study had ended (end of 2004) before this project started, so it was difficult to recontact participants. A total of 607 samples had sufficient DNA for successful SNP genotyping. Table I shows the demographic data for the TENOR cases and the 2 control populations. The TENOR patients with asthma who were genotyped were similar in characteristics to the larger TENOR cohort.

General population controls were obtained by using the Illumina iControlDB client (www.illumina.com) to download genotypes for 3294 white individuals with genotype data available from any of the 3 available HumanHap550 k products (v1, v3, and -2v3). As shown in Table I, only age and sex data are available. Additional control samples for asthma-related quantitative traits were obtained from a separate GWAS for asthma. These 363 phenotyped controls had no personal or family history of asthma and had normal pulmonary function including lack of bronchial hyperresponsiveness or bronchodilator reversibility. Testing also included measures of atopy including total serum IgE levels (Table I). HapMap samples (N = 262) to be used for genetic ancestry check were also downloaded from the iControlDB database (Illumina, Inc) after selecting the HumanHap300_v1 genotyping product.

DNA was isolated by using the protocol described by DNA Genotek, and SNP genotyping was performed by using the Illumina HumanCNV370 BeadChip. The samples were clustered by first applying Illumina's cluster definition, removing samples with call rates less than 0.90, and then reclustering using the samples themselves.

Statistical analysis

PLINK (version 1.06; http://pngu.mgh.harvard.edu/purcell/plink/)[20] was the main software used to perform statistical analysis unless otherwise stated.

Quality control (QC) was applied to cases and controls separately because they were genotyped by using slightly different Illumina products. Genetic ancestry of the TENOR cases was determined using the HapMap 300 k dataset as a reference. Fixed 3 groups clustering and pairwise population concordance of 1.0E-05 based on identity-by-state (IBS) were used to cross-validate ethnic group identity. Subjects were removed if they (1) were not of European white descent, (2) had low genotyping call rates (<95%), (3) were discrepant or ambiguous for genetic sex (heterozygous haploid genotype percentage ≥0.01 or X chromosome homorozygosity F ≥0.9), (4) failed the cryptic relatedness check (PI_HAT > 0.125), or (5) were detected as an outlier (>6 SD for the first or second principal component). After subjects meeting these criteria were deleted, SNPs were deleted if the call rates were low (95%) or were inconsistent with Hardy-Weinberg equilibrium (P < 10E-04). QC was then applied on the subjects and SNPs of merged case-control dataset as done separately. SNPs were also deleted if the minor allele frequency (MAF) was less than 0.05 in cases and controls or the Hardy-Weinberg equilibrium P value was less than .01 in controls only.

Asthma susceptibility was analyzed by comparing the non-Hispanic white TENOR cases to the general population Illumina controls. To reduce population stratification, 4 controls were matched with every 1 case based on pairwise IBS. Principal components were generated by using principal components analysis in EIGENSTRAT (version 3.0; http://genepath.med.harvard.edu/~reich/Software.htm).[21] Sex, age, and significant principal components were used as covariates in the logistic additive model. Genomic control (GC) was applied on P values to reduce population stratification further.[22] A linear model was analyzed in GWAS-identified candidate regions in 473 TENOR cases and 363 phenotyped controls for asthma-related quantitative traits (total serum IgE, % predicted FEV_1, forced vital capacity [FVC], and FEV_1/FVC).

Haploview (http://www.broad.mit.edu/mpg/haploview/) was used to generate linkage disequilibrium plots.[23] Ninety-five percent CIs on D' were used to define blocks.[24] SNAP (version 2.0; http://www.broad.mit.edu/mpg/snap/) was used to generate the association plots.[25] Imputation was performed based on HapMap II CEU genotype data[26] by using MACH (version 1.0; http://www.sph.umich.edu/csg/abecasis/MaCH/index.html).[27] Association of candidate SNPs with nearby gene expression data in lymphocytes was performed based on the GENEVAR dataset (http://www.sanger.ac.uk/humgen/genevar/)[28] by using WGAViewer.[29]

RESULTS

A total of 607 TENOR cases were genotyped with the HumanCNV370 BeadChip. After removal of nonwhite samples (see this article's Fig E1 in the Online Repository at www.jacionline.org) and removal on the basis of the QC criteria, data from 474 patients with asthma were carried forward to analysis. Of the 3294 Illumina white controls downloaded from iControldb, 3,141 Illumina controls passed QC. After merging 474 TENOR cases with 3141 Illumina controls and evaluating the combined QC metrics, 473 cases and 3106 controls were retained. To reduce population stratification, 4 controls were matched with every 1 case on the basis of pairwise IBS; thus, 473 cases and

TABLE I. Demographics (means ± SDs) of subjects in TENOR and Illumina and phenotyped controls

	TENOR cases	Illumina controls	Phenotyped controls
N	473	1892	363
Age (y)	46.9 ± 18.4	31.4 ± 21.9	32.1 ± 10.3
Sex (% female)	63.0	62.5	61.2
Log total IgE (geometric mean)	1.9 ± 0.7 (88.5)	NA	1.3 ± 0.7 (19.6)
FEV_1 (%)	78.5 ± 21.6	NA	97.9 ± 10.7
FVC (%)	89.5 ± 19.9	NA	100.8 ± 11.2
FEV_1/FVC	0.72 ± 0.12	NA	0.82 ± 0.08

Illumina controls were used for GWAS. The Wake Forest phenotyped controls were mainly recruited through the NHLBI Collaborative Study on the Genetics of Asthma and the NHLBI Severe Asthma Research Program and were genotyped as a subset of the NHLBI STAMPEED study.

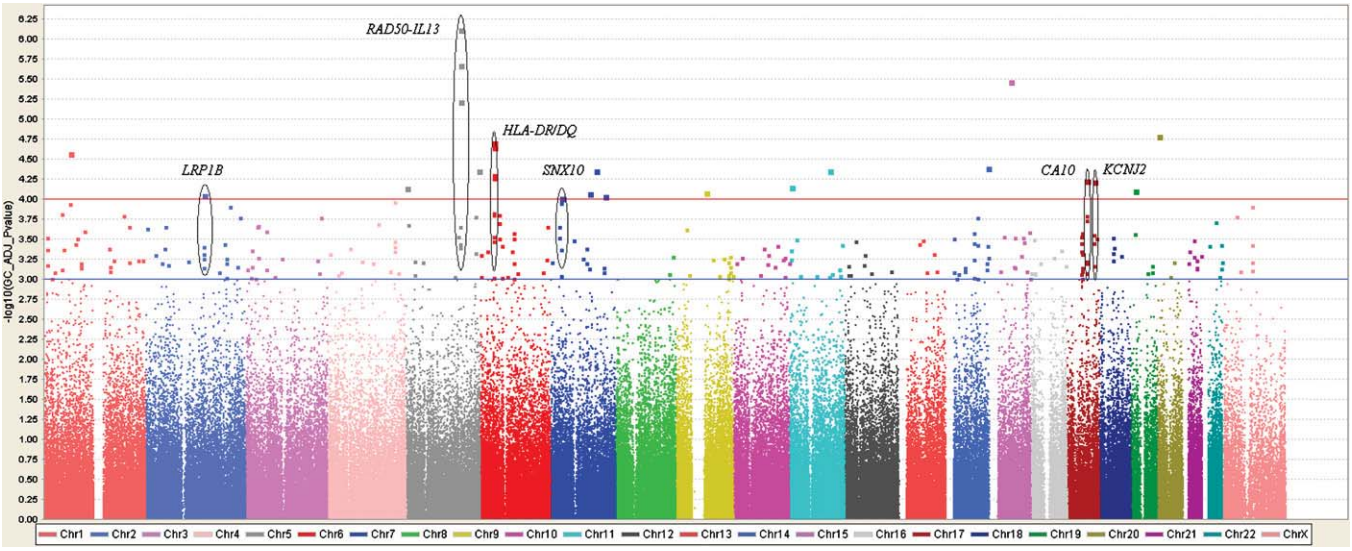

FIG 1. Genome-wide association of 292,443 SNPs in 473 TENOR cases and 1892 Illumina controls. Color scale of the *x-axis* represents chromosomes. Negative logarithm–transformed GC-adjusted *P* values are shown on the *y-axis*.

TABLE II. Association results of 14 SNPs in T_H2 cytokine locus on chromosome 5

No.	SNP	Position	Gene	Alleles (M:m)	MAF	OR (95% CI)	*P* value	Log total IgE	FEV_1/FVC	FEV_1 (%)	FVC (%)
1	rs4143832	131890876	*IL5*	C:A	0.178	1.23 (1.00-1.51)	5.10E-02	4.31E-02	7.01E-01	5.31E-01	8.01E-01
2	rs11739623	131892051	*IL5*	C:T	0.255	0.91 (0.75-1.10)	3.28E-01	4.28E-01	8.14E-01	3.38E-01	3.91E-01
3	rs2079103	131892405	*IL5*	G:T	0.237	1.06 (0.88-1.28)	5.22E-01	2.30E-01	8.84E-01	4.36E-01	6.05E-01
4	rs2706399	131895601	*IL5*	A:G	0.497	1.00 (0.85-1.17)	9.92E-01	9.85E-01	8.28E-01	5.23E-01	4.15E-01
5	rs743562	131900282	*IL5*	C:T	0.423	1.06 (0.89-1.25)	5.22E-01	5.94E-01	5.18E-01	7.35E-01	4.98E-01
6	rs739719	131900764	*IL5*	G:T	0.069	0.79 (0.57-1.11)	1.72E-01	1.20E-01	1.96E-01	9.95E-01	8.02E-01
7	rs2244012	131929124	*RAD50*	T:C	0.212	1.64 (1.36-1.97)	3.04E-07	5.90E-03	3.18E-02	8.64E-02	1.59E-01
8	rs2897443	131957493	*RAD50*	C:A	0.199	1.58 (1.31-1.92)	2.74E-06	1.86E-02	9.75E-02	1.99E-01	2.48E-01
9	rs6871536	131997773	*RAD50*	T:C	0.208	1.60 (1.33-1.94)	9.03E-07	2.61E-03	3.36E-02	1.38E-01	2.58E-01
10	rs2237060	131998784	*RAD50*	A:C	0.425	0.88 (0.74-1.04)	1.22E-01	2.56E-01	1.19E-01	1.16E-01	2.79E-01
11	rs1295686	132023742	*IL13*	G:A	0.198	1.45 (1.19-1.76)	2.21E-04	6.16E-02	2.10E-03	1.84E-03	3.77E-02
12	rs20541	132023863	*IL13*	C:T	0.191	1.44 (1.19-1.76)	2.50E-04	6.06E-02	1.83E-03	2.18E-03	3.69E-02
13	rs2243204	132027393	*IL13*	C:T	0.086	1.69 (1.29-2.21)	1.31E-04	1.67E-03	1.11E-02	1.39E-02	8.10E-02
14	rs2243300	132031985	*IL4*	G:T	0.08	1.51 (1.15-1.99)	3.17E-03	3.14E-02	1.57E-03	7.89E-03	8.58E-02

Alleles (M:m), Major allele:minor allele; *OR,* odds ratio.
Log total IgE, FEV_1/FVC, FEV_1, and FVC are *P* values of asthma-related quantitative traits.

1892 Illumina controls were used for GWAS (see Table I for demographics and this article's Fig E2 in the Online Repository at www.jacionline.org). After QC analysis of the 318,075 common SNPs, 292,443 SNPs were retained for the GWAS.

The GWAS of asthma was performed on 292,443 SNPs of 473 TENOR cases and 1892 Illumina controls with sex, age, and significant principal components as covariates in the logistic additive model (Fig 1). GC was applied to *P* values to reduce

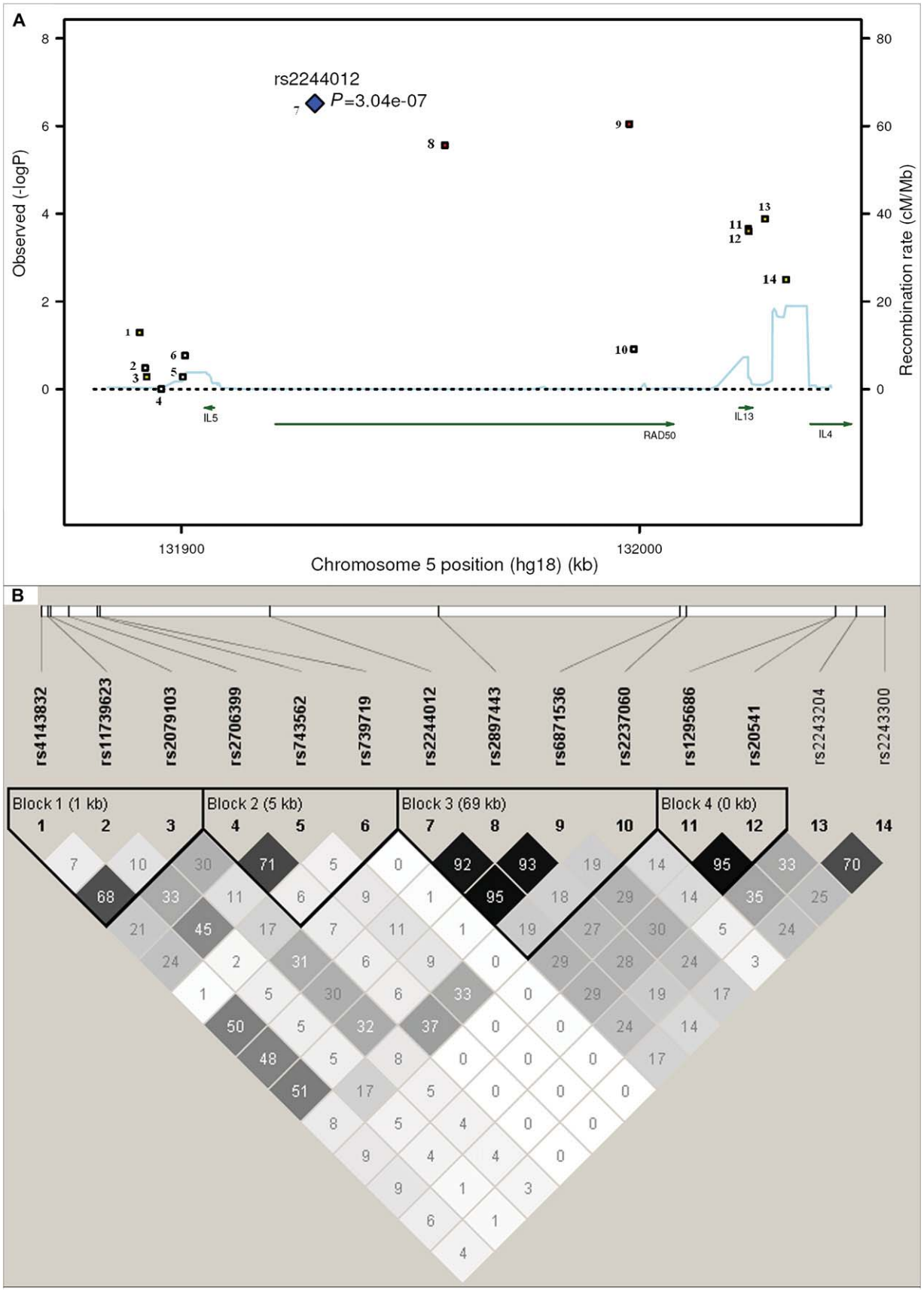

FIG 2. LD and association plot of 14 SNPs in the T_H2 cytokine locus. **A,** Association plot: negative logarithm–transformed *P* values *(left)* and recombination rate *(right)*. **B,** LD plot: r^2 color scheme was used and labeled. 95% CIs on D′ were used to set up blocks.

TABLE III. Association results of 10 of 46 SNPs (with $P \leq .001$) in the HLA-DR/DQ region

No.	SNP	Position	Gene	Alleles (M:m)	MAF	OR (95% CI)	*P* value
1	rs9268542	32492699	*BTNL2*	A:G	0.377	1.40 (1.18-1.65)	8.55E-05
13	rs2239804	32519501	*HLA-DRA*	A:G	0.461	1.43 (1.21-1.68)	2.80E-05
19	rs2395185	32541145	*HLA-DRA*	G:T	0.331	1.40 (1.19-1.66)	8.73E-05
20	rs2516049	32678378	*HLA-DRB1*	A:G	0.319	1.44 (1.22-1.71)	2.62E-05
21	rs660895	32685358	*HLA-DRB1*	A:G	0.202	1.45 (1.19-1.75)	2.02E-04
25	rs1063355	32735692	*HLA-DQB1*	C:A	0.397	0.68 (0.58-0.81)	9.55E-06
26	rs9275141	32759095	*HLA-DQB1*	T:G	0.497	1.37 (1.16-1.61)	1.77E-04
30	rs5000634	32771542	*HLA-DQB1*	T:C	0.386	1.39 (1.18-1.65)	9.16E-05
35	rs9275312	32773706	*HLA-DQB1*	A:G	0.132	1.63 (1.31-2.02)	1.13E-05
46	rs3916765	32793528	*HLA-DQA2*	G:A	0.11	1.50 (1.18-1.90)	9.78E-04

Alleles (M:m), Major allele:minor allele; *BTNL2,* butyrophilin-like 2; *OR,* odds ratio.

population stratification (genomic inflation factor = 1.073 and 1.000 before and after adjustment; see this article's Fig E3 in the Online Repository at www.jacionline.org). In total, 248 SNPs had GC-adjusted *P* values ≤1.0E-03 (see this article's Table E1 in the Online Repository at www.jacionline.org). Focusing on SNPs with a GC-adjusted *P* values ≤1.0E-04 and at least 2 neighboring SNPs (±100 kb) with GC-adjusted *P* values ≤1.0E-03, six regions were identified: *RAD50-IL13* on chromosome 5q31.1, *HLA-DR/DQ* on 6p21.32, low density lipoprotein-related protein 1B on 2q22.1-22.2, sorting nexin 10 on 7p15.2, carbonic anhydrase X on 17q21.33, and potassium inwardly-rectifying channel, subfamily J, member 2 on 17q24.3 (Fig 1; Table E1).

The RAD50-IL13 region had the strongest evidence for association (Table II; Fig 2, *A*) with multiple SNPs in this region strongly associated with asthma susceptibility (rs2244012, rs6871536, and rs2897443 in *RAD50* ranked highly as 1, 2, and 4, respectively, in this study). rs2244012 in intron 2 of *RAD50* had an odds ratio of 1.64 (95% CI, 1.36-1.97; $P = 3.04E-07$; GC-adjusted $P = 7.69E-07$). Three SNPs in or near *IL13* (rs2243204 [3′ downstream], rs20541 [Arg130Gln], and rs1295686 [intron 3]) were also associated with asthma ($P < .001$), but in weak LD ($0.2 < r^2 < 0.3$) with SNPs in *RAD50* (Fig 2, *A and B*). rs2243300, which is ~5 kb upstream of *IL4*, was weakly associated with asthma ($P = .0032$). Six SNPs downstream of *IL5* were not associated with asthma, although they were in weak LD with SNPs in *RAD50* (Table II; Fig 2, *A and B*). Four LD blocks were identified based on 95% CI of D' (Fig 2, *B*).[24] Blocks 1 and 2 were each composed of 3 SNPs downstream of *IL5*. Block 3 was composed of 4 SNPs in the intron of *RAD50*. Block 4 was composed of 2 SNPs in *IL13*.

Linear model analysis was performed with the 14 SNPs of the T_H2 cytokine locus in 473 TENOR cases and 363 phenotyped controls for asthma-related quantitative traits (total serum IgE, FEV_1, FVC, and FEV_1/FVC; Table II). Multiple SNPs in each gene—*RAD50*, *IL13*, and *IL4*, but not *IL5*—showed significant association ($P \leq .05$) with asthma-related quantitative traits.

The HLA-DR/DQ region (Table III; Fig 3, *A*) also showed consistent association with asthma. rs1063355 in the 3′ untranslated region of *HLA-DQB1* had an odds ratio of 0.68 (95% CI, 0.58-0.81; $P = 9.55E-06$; GC-adjusted $P = 1.93E-05$). Ten of the 46 SNPs in the HLA-DR/DQ region had $P \leq .001$ (Table III; Fig 3, *A*). Multiple SNPs in or near butyrophilin-like 2, *HLA-DRA*, *HLA-DRB1*, *HLA-DQB1*, and *HLA-DQA2*, were strongly associated with asthma ($P < 10E-04$). LD is complicated in this region when considering all 46 SNPs (data not shown). One LD block composed of 3 SNPs upstream of *HLA-DQB1* was formed on the basis of the 95% CI of D' of these 10 SNPs (Fig 3, *B*).

Linear model analysis was performed with the 10 SNPs of the HLA-DR/DQ region for asthma-related quantitative traits (Table III). A single SNP, rs1063355, on *HLA-DQB1* showed significant association with asthma-related quantitative traits ($P = .01$, .001, .007, and .05 for total serum IgE, FEV_1, FVC, and FEV_1/FVC, respectively).

DISCUSSION

The highest associated SNP identified in this study was rs2244012 in intron 2 of *RAD50* ($P = 3.04E-07$). In addition, evidence was observed for association with multiple SNPs in the RAD50-IL13 region for asthma susceptibility and asthma related quantitative traits. The protein encoded by *RAD50* is involved in DNA double-strand break repair, and its expression level is constitutively low in most tissues; thus, it has no known function directly related to asthma, although the MER11-RAD50-NBS1 complex has been shown to be involved in somatic hypermutation and gene conversion of immunoglobulin regions.[30] On the contrary, other genes (*IL4*, *IL5*, and *IL13*) in the T_H2 cytokines locus are better candidates on the basis of their biologic functions. Three SNPs in *IL13* in this study were associated with asthma. *IL13* is critical to the pathogenesis of allergen-induced asthma and thus one of the most highly studied and replicated genes in both genome-wide linkage and candidate-gene association studies. rs20541 (Arg130Gln or IL13+4257GA), in the coding region of *IL13*, was also analyzed in this study and has been shown to be associated with asthma[31] and total serum IgE levels.[32] rs1800925 (IL13-1111CT), in the promoter region of *IL13*, has been shown to be associated with asthma[33] and total serum IgE levels.[34] In a GWAS with total serum IgE levels, 4 SNPs in *RAD50* (rs2706347, rs3798135, rs2040704, and rs7737470), have been identified ($P < 10E-04$).[15] These 4 SNPs in *RAD50* were in strong LD with rs1800925 ($0.7 < r^2 < 0.8$) and in weak LD with *rs20541* ($0.2 < r^2 < 0.3$) in *IL13*.[15] These results are consistent with the results of this study because many of the TENOR patients with asthma were recruited from allergists' offices and the population has increased IgE levels.[18] Because the actual functional SNPs cannot be determined purely by their *P* values, it is difficult to dissect the association data of *RAD50* from *IL13* in this study or other genetic studies because of the degree of LD present in this chromosomal region.

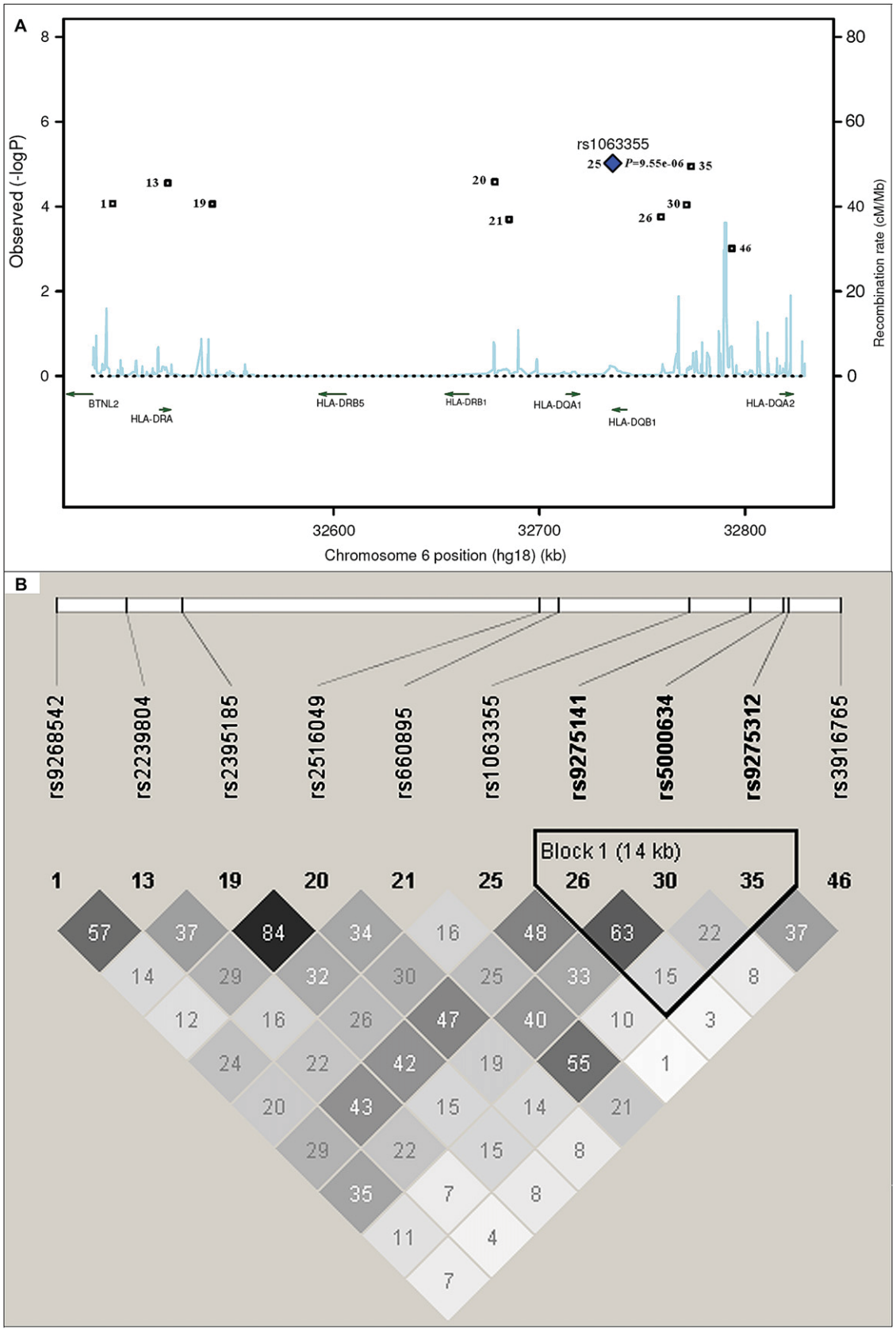

FIG 3. LD and association plot of 10 SNPs in the HLA-DR/DQ region. **A,** Association plot: negative logarithm–transformed *P* values *(left)* and recombination rate *(right)*. **B,** LD plot: r^2 color scheme was used and labeled. 95% CIs on D′ were used to set up blocks. Only 10 of 46 SNPs (with $P \leq .001$) are shown.

In a transgenic mouse study, a T_H2 locus control region (LCR) was identified as the 25-kb fragment at the 3′ end of *Rad50*.[35] An LCR is defined experimentally as regulating the expression of linked genes in a copy number–dependent and tissue-specific manner. The T_H2 LCR is involved in the chromatin configuration to reorganize promoters of *IL4*, *IL5*, and *IL13* in proximity and coregulation of T_H2 cytokine expression.[36] Seven *Rad50* DNase I–hypersensitive sites (RHS1-7) were identified, where RHS4-7 formed the core of the LCR.[37] LCR-C (RHS7) and LCR-B (RHS6) were possible T_H2 cytokine expression enhancers; LCR-A (RHS6) and LCR-O (RHS5) were likely insulators.[38] RHS7 is essential for T_H2 cytokine expression by showing T_H2 specific demethylation after allergen stimulation and intrachromosomal interactions between LCR and the promoters of T_H2 cytokines.[39] Furthermore, RHS6, *Rad50* promoter (RHS2), and *IL5* promoter interacted with IFN-γ (*Ifng*) on a different chromosome, which suggests an interchromosomal regulation of the expression of T_H1/T_H2 cytokines.[40] Although all these experiments were done in mouse, the *RAD50* sequence is highly conserved in the LCR between human being and mouse. With imputation, multiple significant SNPs were found in the LCR (see this article's Table E2 in the Online Repository at www.jacionline.org): rs3798135 ($P = 1.49E-06$, in RHS5/LCR-O), rs12653750 ($P = 1.49E-06$, in RHS6/LCR-A), rs2040704 ($P = 1.33E-06$, in RHS6/LCR-B), and rs2240032 ($P = 6.68E-06$, in RHS7/LCR-C). The association of rs2244012 with the expression levels of *IL13* in lymphocytes from white adults based on the GENEVAR dataset was not significant ($P = 0.176$), but may be a result of small sample size.

Because both a previous GWAS for total serum IgE levels and our GWAS of asthma identified *RAD50*, it appears to be a new candidate gene for asthma. Although it is still possible the signal from *RAD50* is purely a result of its LD with the promoter of *IL13*, *RAD50* deserves to be carefully studied when considering T_H2 cytokine locus.

HLA-DR/DQ also showed consistent association with asthma—for example, rs1063355 in the 3′ untranslated region of *HLA-DQB1* ($P = 9.55E-06$), rs2239804 in intron of *HLA-DRA* ($P = 2.80E-05$), and rs2516049 5′ upstream of *HLA-DRB1* ($P = 2.62E-05$). *HLA-DR/DQ* is part of the HLA class II region, which is one of the most gene/variant-dense regions in the human genome and is associated with many diseases.[41] *HLA-DQB1* and *HLA-DRB1* have been shown to be associated with asthma in multiple independent studies.[42-44] Genetic variants in the HLA-DR/DQ region have also been shown to be highly associated with *HLA-DR/DQ* gene expression, indicating that the association of *HLA-DR/DQ* with disease might be a result of gene expression levels in addition to antigen recognition.[45,46] The association of rs2516049 with asthma in our study and with the expression levels of *HLA-DRB1* ($P = 1.25E-04$) in lymphocytes from white adults based on GENEVAR dataset indicated that the variant might function through expression level changes (see this article's Fig E4 in the Online Repository at www.jacionline.org).[28,29] Imputation identified a SNP with a more significant *P* value, rs3998159 ($P = 1.45E-06$), between *HLA-DQB1* and *HLA-DQA2* (see this article's Table E3 in the Online Repository at www.jacionline.org). It is difficult to determine the functional genes/SNPs in the HLA-DR/DQ region in our study because of the complicated LD pattern in this region. The long-range LD and haplotype analysis based on the MHC Haplotype Project may solve the issue.[47]

Using a GWAS approach, this study is the first to confirm the association of RAD50-IL13 and HLA-DR/DQ regions with asthma susceptibility, regions that have been identified by multiple candidate-gene association studies and 1 genome-wide association study on total serum IgE levels. Our results weakly replicated the findings of the other GWAS: ORM1-like 3 and gasdermin B (*GSDML*; rs7216389) with asthma ($P = .057$); FCER1A (rs2251746) with total serum IgE ($P = .040$); and chitinase 3-like 1 (rs880633) with FEV_1 ($P = .003$), FVC ($P = .031$), and FEV_1/FVC ($P = .040$). rs1588265 ($P = .507$) and rs1544791 ($P = .678$) in *PDE4D* with asthma were not replicated. GWAS of total serum IgE by Weidinger et al[15] identified several SNPs in *RAD50* ($P < 10E-04$). In our study, the most significant SNP in *RAD50* for total serum IgE is rs6871536 ($P = 2.61E-03$). The geometric mean of total serum IgE in the study by Weidinger et al[15] is 42.41 (95% CI, 39.56-45.47). In our study, the geometric mean of total serum IgE is higher, 48.94 (95% CI, 43.04-55.65). The difference in the total serum IgE distribution and the relatively small sample size in our study may lead to the difference of significant levels between these 2 studies.

The potential for false-negative results could not be avoided in this study because of the relatively small sample size (473 cases), which may also be the reason that although significance levels of 10^{-7} (E-07) were observed, no SNP reached the Bonferroni-adjusted multiple test criterion ($P = .05/292,443 = 1.71E-07$). However, evidence for multiple SNPs was observed in our results in this comprehensively phenotyped relatively homogeneous cohort of patients with difficult-to-treat asthma from the larger TENOR study. Our control datasets (general population and phenotyped controls) both have some limitations. They were both significantly younger (Table I) than TENOR cases, making our results a little conservative because some controls might become asthma cases in the future. Genotyping confirmation and fine-mapping of candidate regions were impossible because the Illumina controls were from a public database, but our approach compensated for this by using imputation. Population stratification was relatively strong between TENOR cases and Illumina 550k controls.

This GWAS confirmed the important role of T_H2 cytokine and antigen presentation genes in asthma at a genome-wide level. Furthermore, these findings will stimulate more comprehensive research (eg, resequencing, long-range LD, epistasis, epigenetics, copy number variant, and function) on these 2 regions because of their functional importance and structural complexity.

We thank Dr Elizabeth J. Ampleford for analytical assistance. We also acknowledge the TENOR/SARP/CSGA/STAMPEED Study Group and the TENOR/SARP/CSGA/STAMPEED participants who contributed DNA samples.

Clinical implications: A GWAS of asthma identifies RAD50-IL13 and HLA-DR/DQ. These findings will stimulate more comprehensive research on these genes because of their structural complexity and functional importance in the pathogenesis of asthma.

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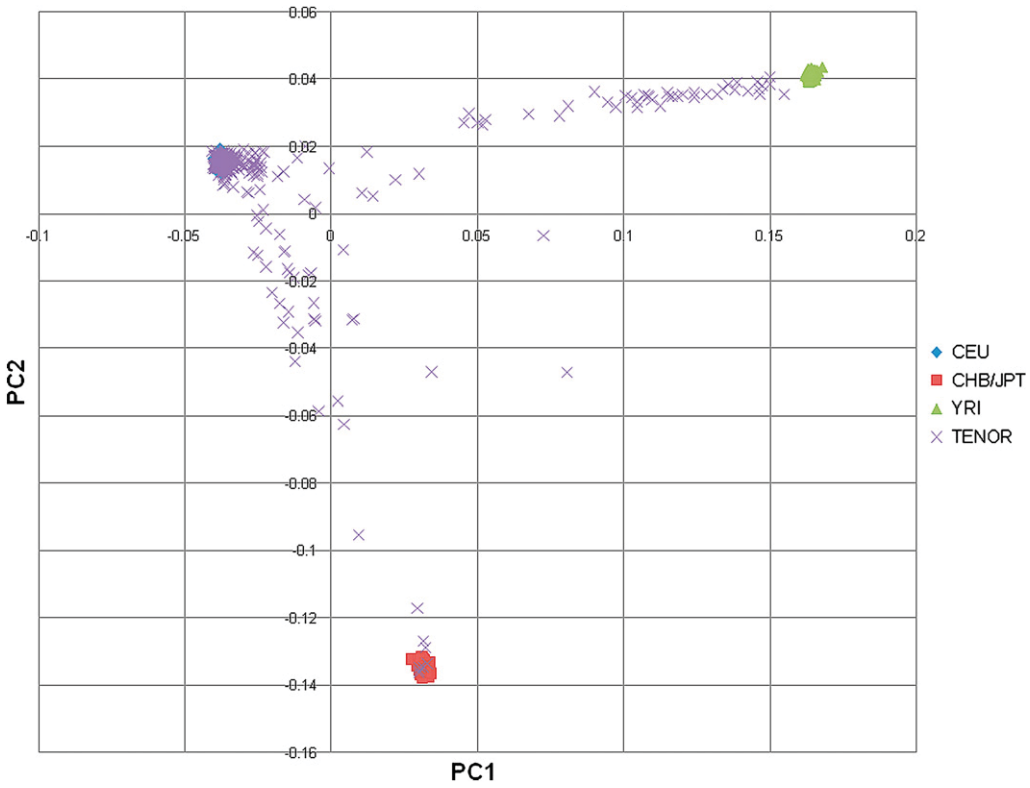

FIG E1. Cluster plot of 607 TENOR cases and 262 HapMap samples. *PC1* and *PC2* are the first and second principle component, respectively.

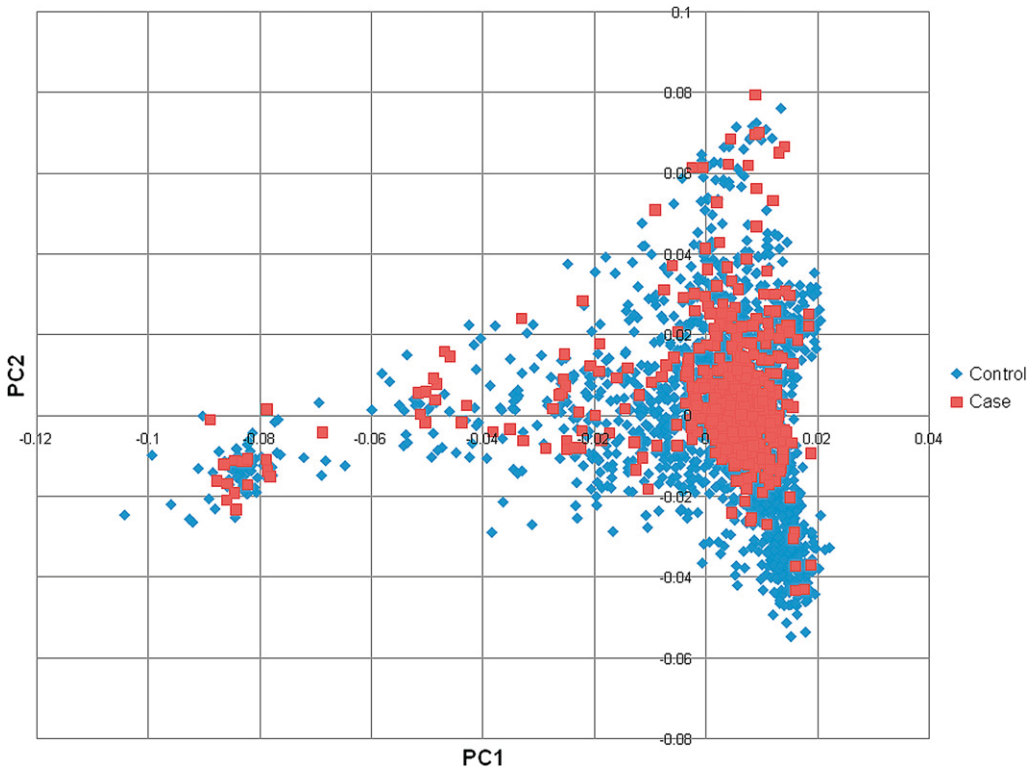

FIG E2. Principle components plot of 473 TENOR cases and 1892 Illumina controls. *PC1* and *PC2* are the first and second principle component, respectively.

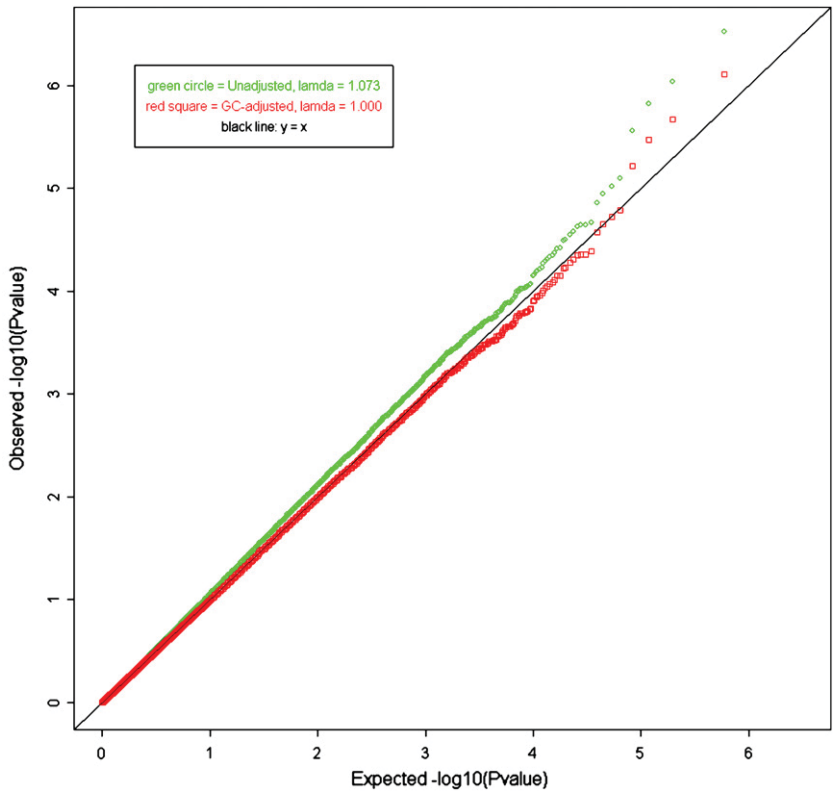

FIG E3. GWAS qq-plot of 292,443 SNPs of 473 TENOR cases and 1,892 Illumina controls. Negative logarithm–transformed expected *P* values are shown on the *x-axis*. Negative logarithm–transformed observed *P* values are shown on the *y-axis*.

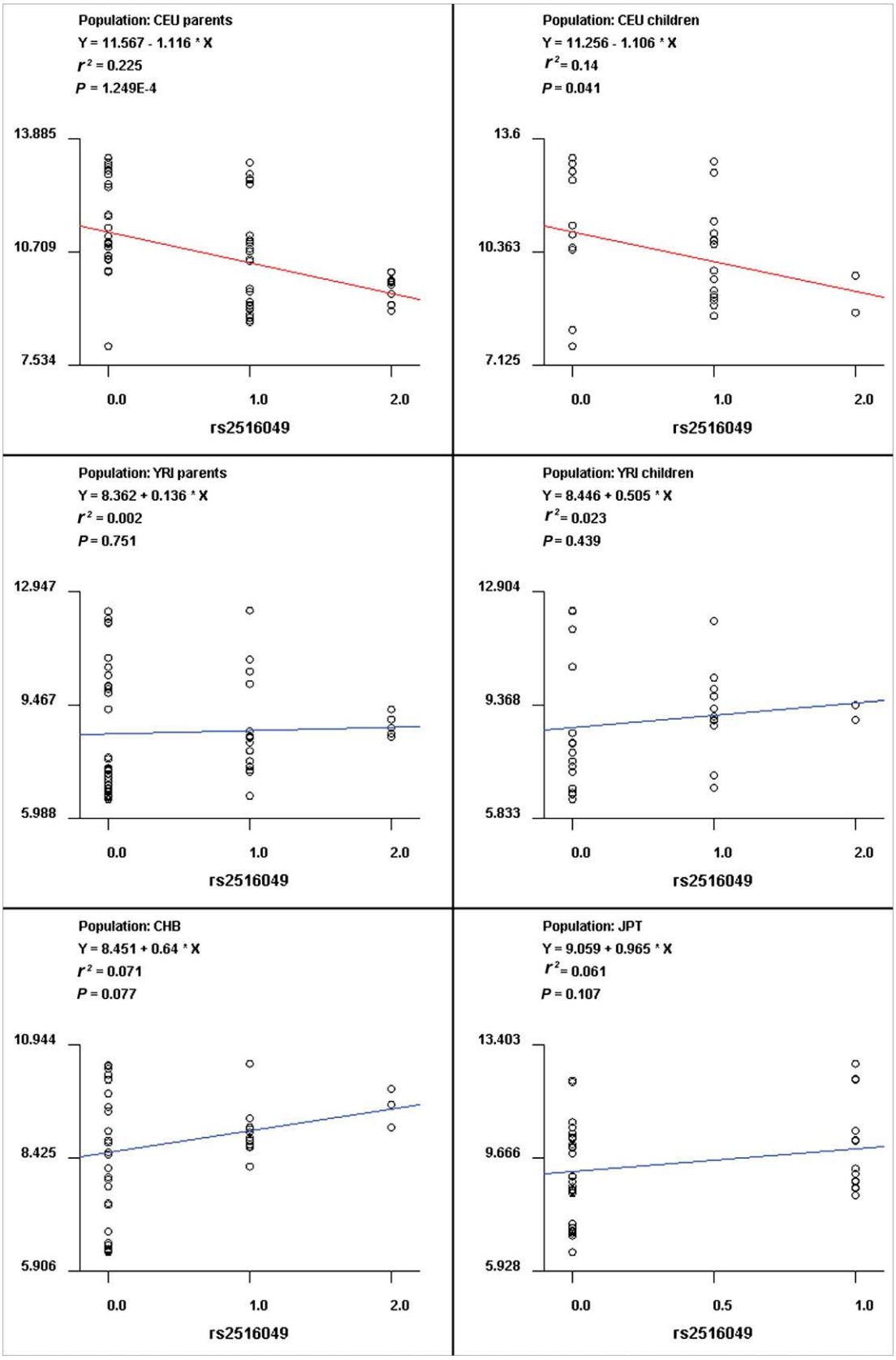

FIG E4. Association of rs2516049 with the expression of *HLA-DRB1* in lymphocytes based on GENEVAR dataset. *X-axis* represents copy numbers of minor allele of rs2516049. *Y-axis* represents the expression levels of *HLA-DRB1* in lymphocytes.

TABLE E1. Association results of 248 SNPs with GC-adjusted *P* values ≤1.0E-03

SNP	UNADJ *P* value	GC-ADJ *P* value	Chr	Coordinate	Gene	Location
rs2244012	3.04E-07	7.69E-07	5	131929124	*RAD50*	Intron
rs6871536	9.03E-07	2.13E-06	5	131997773	*RAD50*	Intron
rs17525472	1.50E-06	3.41E-06	15	49756960	*SCG3*	Flanking_5UTR
rs2897443	2.74E-06	5.99E-06	5	131957493	*RAD50*	Intron
rs4815617	7.92E-06	1.62E-05	20	3775309	*KIAA1271*	Flanking_5UTR
rs1063355	9.55E-06	1.93E-05	6	32735692	*HLA-DQB1*	3UTR
rs9275312	1.13E-05	2.25E-05	6	32773706	*HLA-DQB1*	Flanking_5UTR
rs10493343	1.37E-05	2.69E-05	1	63486112	*FOXD3*	Flanking_5UTR
rs8020818	2.14E-05	4.09E-05	14	100753214	FLJ41170	Flanking_3UTR
rs6861032	2.29E-05	4.36E-05	5	174833658	*SFXN1*	Flanking_5UTR
rs17275283	2.30E-05	4.39E-05	11	96347024	*JRKL*	Flanking_3UTR
rs6958325	2.33E-05	4.43E-05	7	110464892	*LRRN3*	Flanking_5UTR
rs2516049	2.62E-05	4.95E-05	6	32678378	*HLA-DRB1*	Flanking_5UTR
rs2239804	2.80E-05	5.26E-05	6	32519501	*HLA-DRA*	Intron
rs967676	3.18E-05	5.92E-05	17	47315308	*CA10*	Intron
rs723498	3.25E-05	6.05E-05	17	65787127	*KCNJ2*	Flanking_3UTR
rs16909520	3.81E-05	7.01E-05	11	5041830	*OR52E2*	Flanking_5UTR
rs13159461	3.89E-05	7.16E-05	5	1256437	*SLC6A19*	Intron
rs2277968	4.27E-05	7.80E-05	19	9932669	*COL5A3*	Intron
rs1411164	4.46E-05	8.14E-05	9	72844892	*TRPM3*	Intron
rs11770226	4.69E-05	8.52E-05	7	94923367	*PON2*	Flanking_5UTR
rs10496855	4.90E-05	8.88E-05	2	141354850	*LRP1B*	Intron
rs326234	5.12E-05	9.26E-05	7	130526092	*MKLN1*	Flanking_5UTR
rs1859600	5.38E-05	9.69E-05	7	26509841	*SNX10*	Flanking_3UTR
rs3180361	5.83E-05	1.04E-04	7	26503438	*SNX10*	Flanking_3UTR
rs359486	6.11E-05	1.09E-04	4	163127283	*FSTL5*	Intron
rs757393	6.26E-05	1.12E-04	7	26498670	*SNX10*	Flanking_3UTR
rs1328589	6.50E-05	1.16E-04	1	63447502	*FOXD3*	Flanking_5UTR
rs646297	6.98E-05	1.24E-04	23	71455300	*HDAC8*	Flanking_3UTR
rs3181096	7.12E-05	1.26E-04	2	204278337	*CD28*	Flanking_5UTR
rs9268542	8.55E-05	1.49E-04	6	32492699	*BTNL2*	Flanking_5UTR
rs2395185	8.73E-05	1.52E-04	6	32541145	*HLA-DRA*	Flanking_3UTR
rs655198	8.87E-05	1.55E-04	1	42098604	*HIVEP3*	Intron
rs2280229	9.15E-05	1.59E-04	6	45651316	*RUNX2*	Flanking_3UTR
rs5000634	9.16E-05	1.59E-04	6	32771542	*HLA-DQB1*	Flanking_5UTR
rs11079992	9.24E-05	1.61E-04	17	47572536	*CA10*	Intron
rs3001156	9.46E-05	1.64E-04	1	192817561	*CDC73*	Flanking_3UTR
rs4867956	9.54E-05	1.66E-04	5	169676190	*LOC257358*	Flanking_5UTR
rs5928535	9.65E-05	1.67E-04	23	34313383	*TMEM47*	Flanking_3UTR
rs6779474	9.90E-05	1.71E-04	3	182738502	*SOX2*	Flanking_5UTR
rs7144274	9.94E-05	1.72E-04	14	77695406	*ADCK1*	Flanking_3UTR
rs1916804	9.98E-05	1.73E-04	2	228516940	*WDR69*	Flanking_3UTR
rs2938140	1.06E-04	1.83E-04	17	47531500	*CA10*	Intron
rs362112	1.14E-04	1.95E-04	22	33793994	*RAXLX*	Intron
rs9296461	1.19E-04	2.03E-04	6	45659449	*RUNX2*	Flanking_3UTR
rs6848139	1.21E-04	2.07E-04	4	123614491	*IL2*	Flanking_5UTR
rs6860112	1.26E-04	2.14E-04	5	4189154	*IRX1*	Flanking_3UTR
rs9810311	1.29E-04	2.19E-04	3	31456330	*STT3B*	Flanking_5UTR
rs4953456	1.30E-04	2.20E-04	2	47144074	*TTC7A*	Intron
rs643930	1.30E-04	2.21E-04	1	206224964	*PLXNA2*	Flanking_3UTR
rs6551207	1.30E-04	2.21E-04	3	27527986	*SLC4A7*	Flanking_5UTR
rs9885995	1.31E-04	2.22E-04	7	20579891	*ABCB5*	Flanking_5UTR
rs2243204	1.31E-04	2.23E-04	5	132027393	*IL13*	Flanking_3UTR
rs9346917	1.32E-04	2.24E-04	6	162834976	*PARK2*	Flanking_5UTR
rs12995456	1.39E-04	2.35E-04	2	2573621	*MYT1L*	Flanking_5UTR
rs12352086	1.41E-04	2.39E-04	9	25707537	*TUSC1*	Flanking_5UTR
rs770918	1.49E-04	2.52E-04	1	98701525	*SNX7*	Flanking_5UTR
rs2329020	1.52E-04	2.56E-04	3	49660077	*BSN*	Intron
rs1542112	1.55E-04	2.61E-04	15	96669517	FLJ39743	Flanking_3UTR
rs8020795	1.59E-04	2.67E-04	14	67559788	*RAD51L1*	Intron
rs525247	1.60E-04	2.69E-04	6	81696055	*BCKDHB*	Flanking_3UTR
rs931992	1.61E-04	2.70E-04	17	35074961	*TCAP*	Flanking_5UTR

(Continued)

TABLE E1. *(Continued)*

SNP	UNADJ *P* value	GC-ADJ *P* value	Chr	Coordinate	Gene	Location
rs2967675	1.64E-04	2.74E-04	19	8650484	*MGC33407*	Flanking_3UTR
rs141155	1.66E-04	2.78E-04	17	65865187	*KCNJ2*	Flanking_3UTR
rs9275141	1.77E-04	2.94E-04	6	32759095	*HLA-DQB1*	Flanking_5UTR
rs2056317	1.77E-04	2.95E-04	15	35350843	*MEIS2*	Flanking_5UTR
rs11746935	1.78E-04	2.97E-04	5	127650646	*FBN2*	Intron
rs9906612	1.80E-04	3.00E-04	17	34801157	*FBXL20*	Intron
rs10233470	1.83E-04	3.04E-04	7	20525526	*ITGB8*	Flanking_3UTR
rs12324805	1.84E-04	3.06E-04	15	80139255	*RKHD3*	Flanking_5UTR
rs1029322	1.85E-04	3.08E-04	1	7318619	*CAMTA1*	Intron
rs456084	1.86E-04	3.08E-04	15	60404524	FLJ38723	Flanking_5UTR
rs7241842	1.86E-04	3.08E-04	18	33126739	*BRUNOL4*	Intron
rs1135889	1.86E-04	3.09E-04	17	71437716	*ACOX1*	Flanking_3UTR
rs10948239	1.86E-04	3.09E-04	6	45644058	*RUNX2*	Flanking_3UTR
rs996812	1.87E-04	3.10E-04	1	81229634	*LPHN2*	Flanking_5UTR
rs11701	1.88E-04	3.13E-04	14	20231893	*ANG*	Coding
rs556458	1.90E-04	3.15E-04	6	81687679	*BCKDHB*	Flanking_3UTR
rs10500350	1.93E-04	3.20E-04	16	7170644	*A2BP1*	Intron
rs1541533	1.94E-04	3.21E-04	11	17052787	*RNU14*	3UTR
rs17623690	1.99E-04	3.29E-04	13	58702026	*DIAPH3*	Flanking_3UTR
rs7456530	2.00E-04	3.31E-04	7	56011943	*GBAS*	Intron
rs2830865	2.00E-04	3.31E-04	21	27649571	*ADAMTS5*	Flanking_5UTR
rs3782309	2.02E-04	3.34E-04	12	26750663	*ITPR2*	Intron
rs660895	2.02E-04	3.34E-04	6	32685358	*HLA-DRB1*	Flanking_5UTR
rs359512	2.06E-04	3.41E-04	4	163100537	*FSTL5*	Intron
rs4601994	2.13E-04	3.51E-04	15	84235520	*KLHL25*	Flanking_5UTR
rs7214151	2.15E-04	3.55E-04	17	34761298	*FBXL20*	Intron
rs1956534	2.17E-04	3.56E-04	14	67963825	*RAD51L1*	Intron
rs312729	2.18E-04	3.58E-04	17	65818432	*KCNJ2*	Flanking_3UTR
rs6696780	2.21E-04	3.63E-04	1	76504495	*ST6GALNAC3*	Intron
rs1295686	2.21E-04	3.63E-04	5	132023742	*IL13*	Intron
rs7577607	2.25E-04	3.69E-04	2	192414794	*SDPR*	Intron
rs9563026	2.26E-04	3.71E-04	13	50591509	*GUCY1B2*	Flanking_5UTR
rs10146353	2.27E-04	3.72E-04	14	77705251	*NRXN3*	Flanking_5UTR
rs2307127	2.28E-04	3.73E-04	11	128817282	*BARX2*	Intron
rs739107	2.29E-04	3.76E-04	22	47195099	*FAM19A5*	Flanking_5UTR
rs16988492	2.31E-04	3.79E-04	23	72479814	*CDX4*	Flanking_5UTR
rs1543540	2.32E-04	3.81E-04	14	101867808	*C14orf131*	5UTR
rs2111996	2.33E-04	3.81E-04	10	107461332	*SORCS3*	Flanking_3UTR
rs5992495	2.33E-04	3.81E-04	22	18262984	*TXNRD2*	Coding
rs2025753	2.37E-04	3.87E-04	6	51805526	*PKHD1*	Intron
rs45426	2.39E-04	3.91E-04	4	163113553	*FSTL5*	Intron
rs2380945	2.39E-04	3.91E-04	2	141384793	*LRP1B*	Intron
rs20541	2.50E-04	4.07E-04	5	132023863	*IL13*	Coding
rs1444393	2.50E-04	4.08E-04	18	35540370	*BRUNOL4*	Flanking_5UTR
rs11765081	2.53E-04	4.13E-04	7	88312832	*MGC26647*	Flanking_5UTR
rs14138	2.56E-04	4.16E-04	2	46267950	*PRKCE*	3UTR
rs983789	2.57E-04	4.18E-04	1	157862306	*APCS*	Flanking_3UTR
rs904132	2.57E-04	4.19E-04	4	55496865	*KDR*	Flanking_3UTR
rs9299508	2.58E-04	4.20E-04	10	73213459	*CDH23*	Intron
rs1544412	2.61E-04	4.24E-04	7	26465493	*SNX10*	Flanking_3UTR
rs6577395	2.61E-04	4.25E-04	1	6914512	*CAMTA1*	Intron
rs10951140	2.62E-04	4.26E-04	7	26498245	*SNX10*	Flanking_3UTR
rs688540	2.63E-04	4.27E-04	1	47775034	*FOXD2*	Flanking_3UTR
rs2189556	2.67E-04	4.33E-04	7	26461733	*SNX10*	Flanking_3UTR
rs12574869	2.70E-04	4.37E-04	11	5029677	*OR52J3*	Flanking_3UTR
rs1579333	2.73E-04	4.42E-04	16	73710475	*LDHD*	Flanking_5UTR
rs9874701	2.74E-04	4.43E-04	3	16130293	*GALNTL2*	Flanking_5UTR
rs2823048	2.76E-04	4.47E-04	21	15384139	*NRIP1*	Flanking_5UTR
rs359508	2.77E-04	4.49E-04	4	163103214	*FSTL5*	Intron
rs179988	2.79E-04	4.51E-04	6	16446200	*ATXN1*	Intron
rs7208487	2.79E-04	4.51E-04	17	34796975	*FBXL20*	Intron
rs1350406	2.79E-04	4.52E-04	6	77542029	*HTR1B*	Flanking_3UTR

(Continued)

TABLE E1. *(Continued)*

SNP	UNADJ *P* value	GC-ADJ *P* value	Chr	Coordinate	Gene	Location
rs315791	2.94E-04	4.74E-04	5	169668498	*LCP2*	Flanking_5UTR
rs12373339	2.94E-04	4.75E-04	18	32632020	*C18orf10*	Intron
rs1877031	3.00E-04	4.83E-04	17	35067606	*STARD3*	Coding
rs1474454	3.03E-04	4.88E-04	17	36045007	*SMARCE1*	Intron
rs1873288	3.03E-04	4.88E-04	13	84779125	*SLITRK6*	Flanking_3UTR
rs11938388	3.05E-04	4.90E-04	4	7169428	*GRPEL1*	Flanking_5UTR
rs511625	3.05E-04	4.91E-04	2	141066570	*LRP1B*	Intron
rs1530758	3.10E-04	4.99E-04	2	23212606	*UBXD4*	Flanking_5UTR
rs10783425	3.11E-04	4.99E-04	12	49916559	*DAZAP2*	Flanking_5UTR
rs926929	3.15E-04	5.07E-04	10	83837968	*NRG3*	Intron
rs4959689	3.16E-04	5.07E-04	6	2562121	*C6orf195*	Flanking_3UTR
rs11635084	3.16E-04	5.08E-04	15	76473878	*IREB2*	Flanking_5UTR
rs2838906	3.19E-04	5.11E-04	21	45646335	*COL18A1*	Flanking_5UTR
rs9966349	3.24E-04	5.20E-04	18	53442584	*NARS*	Intron
rs4909638	3.28E-04	5.25E-04	8	138323508	*C8ORFK32*	Flanking_3UTR
rs2830863	3.32E-04	5.31E-04	21	27649080	*ADAMTS5*	Flanking_5UTR
rs3750340	3.32E-04	5.31E-04	9	130812210	*SH3GLB2*	Intron
rs9417254	3.36E-04	5.37E-04	10	20055938	*PLXDC2*	Flanking_5UTR
rs2275593	3.36E-04	5.38E-04	14	103709764	*TDRD9*	Flanking_3UTR
rs9789945	3.36E-04	5.38E-04	3	31452286	*STT3B*	Flanking_5UTR
rs7896565	3.39E-04	5.42E-04	10	123382368	*FGFR2*	Flanking_5UTR
rs8056241	3.40E-04	5.43E-04	16	55685889	*CPNE2*	Intron
rs1549709	3.49E-04	5.56E-04	2	141375997	*LRP1B*	Intron
rs6795028	3.50E-04	5.58E-04	3	88563780	*C3orf38*	Flanking_3UTR
rs957781	3.51E-04	5.60E-04	2	196500819	*DNAH7*	Intron
rs12338788	3.53E-04	5.63E-04	9	115253879	*RGS3*	Flanking_5UTR
rs10485961	3.53E-04	5.63E-04	7	78977339	*MAGI2*	Flanking_5UTR
rs4902538	3.55E-04	5.66E-04	14	67494562	*RAD51L1*	Intron
rs1901548	3.56E-04	5.68E-04	6	159818518	FLJ27255	Flanking_3UTR
rs1861828	3.58E-04	5.71E-04	9	89434951	*DAPK1*	Intron
rs4523612	3.61E-04	5.74E-04	10	120273282	*PRLHR*	Flanking_3UTR
rs727152	3.61E-04	5.75E-04	11	3976341	*STIM1*	Intron
rs2066381	3.64E-04	5.79E-04	1	239062050	*RGS7*	Intron
rs3897638	3.64E-04	5.80E-04	18	33151448	*BRUNOL4*	Intron
rs2834280	3.67E-04	5.84E-04	21	34150372	*ITSN1*	Intron
rs986032	3.67E-04	5.84E-04	1	168549668	*SCYL1BP1*	Flanking_5UTR
rs1769807	3.72E-04	5.91E-04	1	229718014	*TSNAX*	Flanking_5UTR
rs4621354	3.74E-04	5.94E-04	3	175070962	*NLGN1*	Intron
rs6535363	3.74E-04	5.94E-04	4	83781593	*SCD5*	Flanking_3UTR
rs203066	3.74E-04	5.95E-04	17	47349497	*CA10*	Intron
rs3917254	3.79E-04	6.01E-04	2	102142950	*IL1R1*	Intron
rs4866207	3.82E-04	6.07E-04	5	20700523	*CDH18*	Flanking_5UTR
rs2866823	3.87E-04	6.14E-04	20	39912917	*PTPRT*	Flanking_3UTR
rs202124	3.89E-04	6.17E-04	17	47342798	*CA10*	Intron
rs134774	3.89E-04	6.17E-04	22	49427626	*ARSA*	Flanking_5UTR
rs7719641	3.89E-04	6.17E-04	5	41360498	*PLCXD3*	Intron
rs10760397	3.89E-04	6.17E-04	9	127173028	*GAPVD1*	Flanking_3UTR
rs723923	3.90E-04	6.18E-04	23	72267781	*LOC340529*	Flanking_5UTR
rs7054904	3.90E-04	6.18E-04	23	72274502	*LOC340529*	Flanking_5UTR
rs861475	3.90E-04	6.19E-04	1	206118011	*CD34*	Flanking_3UTR
rs208358	3.91E-04	6.19E-04	7	2740131	*GNA12*	Intron
rs6962263	3.96E-04	6.26E-04	7	88328758	*MGC26647*	Flanking_5UTR
rs902810	3.96E-04	6.27E-04	14	98537686	*BCL11B*	Flanking_3UTR
rs2822687	3.98E-04	6.29E-04	21	14775306	*SAMSN1*	Flanking_3UTR
rs10493817	3.98E-04	6.30E-04	1	88899475	*PKN2*	Flanking_5UTR
rs6719500	3.98E-04	6.30E-04	2	196533647	*DNAH7*	Coding
rs7393606	3.98E-04	6.30E-04	10	134906487	*VENTX*	Flanking_3UTR
rs1244459	3.99E-04	6.31E-04	10	7968246	*ATP5C1*	Flanking_3UTR
rs7688489	4.00E-04	6.32E-04	4	109906763	*AGXT2L1*	Flanking_5UTR
rs6544127	4.00E-04	6.33E-04	2	38073146	*FAM82A*	Intron
rs767325	4.01E-04	6.34E-04	17	47260643	*CA10*	Intron
rs2106365	4.02E-04	6.36E-04	16	22830079	*HS3ST2*	Intron

(Continued)

TABLE E1. *(Continued)*

SNP	UNADJ *P* value	GC-ADJ *P* value	Chr	Coordinate	Gene	Location
rs10485285	4.03E-04	6.38E-04	6	81535326	*BCKDHB*	Flanking_3UTR
rs10801687	4.13E-04	6.52E-04	1	89079849	*PKN2*	Flanking_3UTR
rs1019595	4.14E-04	6.54E-04	10	82575930	*SH2D4B*	Flanking_3UTR
rs867389	4.19E-04	6.60E-04	1	6907656	*CAMTA1*	Intron
rs10875660	4.20E-04	6.63E-04	12	46220298	FLJ21908	Flanking_3UTR
rs9677948	4.23E-04	6.67E-04	2	55290438	FLJ31438	Coding
rs7304994	4.30E-04	6.77E-04	12	8883237	*A2ML1*	Intron
rs12601221	4.38E-04	6.89E-04	17	65919990	*KCNJ2*	Flanking_3UTR
rs889608	4.40E-04	6.91E-04	16	85895044	*FBXO31*	Flanking_3UTR
rs2041992	4.42E-04	6.94E-04	19	51216311	*PGLYRP1*	Intron
rs2273866	4.44E-04	6.98E-04	9	130742712	*PHYHD1*	Coding
rs7623955	4.44E-04	6.98E-04	3	16014062	*ANKRD28*	Flanking_5UTR
rs875339	4.46E-04	7.00E-04	15	58883347	*RORA*	Intron
rs1507741	4.47E-04	7.02E-04	1	161224435	*RGS4*	Flanking_5UTR
rs10883109	4.48E-04	7.04E-04	10	100247350	*HPSE2*	Intron
rs6738615	4.52E-04	7.10E-04	2	222599119	*PAX3*	Flanking_3UTR
rs2933192	4.55E-04	7.13E-04	14	46456191	*MAMDC1*	Intron
rs3738795	4.59E-04	7.20E-04	1	90139102	*LRRC8D*	Intron
rs1565922	4.63E-04	7.25E-04	17	35084561	*PERLD1*	Intron
rs205764	4.66E-04	7.30E-04	7	130248776	*KLF14*	Flanking_5UTR
rs10496858	4.66E-04	7.30E-04	2	141356115	*LRP1B*	Intron
rs289107	4.66E-04	7.30E-04	15	60417907	FLJ38723	Flanking_5UTR
rs2070393	4.66E-04	7.31E-04	21	34160957	*ITSN1*	Intron
rs1575847	4.71E-04	7.37E-04	7	94308081	*SGCE*	Flanking_5UTR
rs6007798	4.71E-04	7.38E-04	22	46860129	*LOC388915*	Flanking_5UTR
rs3761353	4.75E-04	7.43E-04	21	34193743	*ATP5O*	Flanking_3UTR
rs3197999	4.82E-04	7.54E-04	3	49696536	*MST1*	Coding
rs1565611	4.85E-04	7.58E-04	14	98543918	*BCL11B*	Flanking_3UTR
rs716066	4.88E-04	7.63E-04	11	120721777	*SC5DL*	Flanking_3UTR
rs606850	4.91E-04	7.66E-04	1	42047721	*HIVEP3*	Intron
rs4684448	4.91E-04	7.66E-04	3	4871495	*ITPR1*	Flanking_3UTR
rs1475091	4.97E-04	7.75E-04	23	71490721	*HDAC8*	Intron
rs3859956	5.08E-04	7.92E-04	23	43738241	*NDP*	Flanking_5UTR
rs4657210	5.12E-04	7.97E-04	1	160854047	*DDR2*	Flanking_5UTR
rs2271308	5.13E-04	7.99E-04	17	35071008	*STARD3*	Intron
rs462954	5.14E-04	8.00E-04	13	91169091	*GPC5*	Intron
rs1003385	5.17E-04	8.04E-04	12	114236286	*TBX3*	Flanking_5UTR
rs1552741	5.18E-04	8.05E-04	14	46414182	*MAMDC1*	Intron
rs4600441	5.18E-04	8.07E-04	15	25127607	*GABRG3*	Flanking_5UTR
rs2217008	5.19E-04	8.07E-04	4	153169194	*PET112L*	Flanking_5UTR
rs7601	5.20E-04	8.09E-04	15	89310596	*PRC1*	3UTR
rs943997	5.23E-04	8.13E-04	14	20535329	FLJ20859	Flanking_3UTR
rs547311	5.24E-04	8.15E-04	7	130248994	*KLF14*	Flanking_5UTR
rs13131255	5.25E-04	8.16E-04	4	31806809	*PCDH7*	Flanking_3UTR
rs730489	5.27E-04	8.18E-04	6	151441584	*MTHFD1L*	Intron
rs12685378	5.29E-04	8.22E-04	9	130787532	*NUP188*	Intron
rs9571705	5.31E-04	8.25E-04	13	66451841	*PCDH9*	Intron
rs311384	5.32E-04	8.27E-04	19	52147155	*GRLF1*	Intron
rs12464787	5.35E-04	8.31E-04	2	179148275	*TTN*	Coding
rs4073051	5.37E-04	8.34E-04	1	24780002	*C1orf130*	Intron
rs2293700	5.38E-04	8.35E-04	19	40688220	*ZD52F10*	Intron
rs203049	5.39E-04	8.36E-04	17	47433988	*CA10*	Intron
rs4985019	5.43E-04	8.42E-04	16	9019717	*USP7*	Flanking_5UTR
rs2054892	5.46E-04	8.47E-04	3	178042453	*TBL1XR1*	Flanking_3UTR
rs2273508	5.48E-04	8.50E-04	6	90034567	*GABRR2*	Intron
rs7664958	5.50E-04	8.52E-04	4	172506527	*AADAT*	Flanking_5UTR
rs11176241	5.52E-04	8.55E-04	12	65194084	*HELB*	Flanking_3UTR
rs2294622	5.53E-04	8.56E-04	16	1536260	*C16orf30*	Intron
rs2004375	5.53E-04	8.58E-04	8	130071912	*CCDC26*	Flanking_3UTR
rs1872901	5.57E-04	8.63E-04	11	103294671	*PDGFD*	Intron
rs7205853	5.59E-04	8.66E-04	16	10435114	*ATF7IP2*	Intron
rs10483393	5.60E-04	8.67E-04	14	31530235	*C14orf128*	Flanking_3UTR

(Continued)

TABLE E1. *(Continued)*

SNP	UNADJ *P* value	GC-ADJ *P* value	Chr	Coordinate	Gene	Location
rs2061342	5.67E-04	8.77E-04	17	34659183	*FBXL20*	Flanking_3UTR
rs7310659	5.75E-04	8.89E-04	12	14201016	*GRIN2B*	Flanking_5UTR
rs3861866	5.76E-04	8.89E-04	9	127060695	*GAPVD1*	Flanking_5UTR
rs6451870	5.77E-04	8.91E-04	5	20686228	*CDH18*	Flanking_5UTR
rs4692346	5.77E-04	8.92E-04	4	25681683	*KIAA0746*	Flanking_5UTR
rs10995190	5.79E-04	8.95E-04	10	63948688	*ZNF365*	Intron
rs13285154	5.82E-04	8.98E-04	9	31495016	*ACO1*	Flanking_5UTR
rs1894814	5.83E-04	9.00E-04	12	8880044	*A2ML1*	Intron
rs10819043	5.83E-04	9.01E-04	9	127077066	*GAPVD1*	Intron
rs10235248	5.92E-04	9.13E-04	7	26470884	*SNX10*	Flanking_3UTR
rs948445	5.92E-04	9.13E-04	11	67171068	*ACY3*	Coding
rs11029745	5.93E-04	9.14E-04	11	26916960	*LOC387758*	Flanking_5UTR
rs4074186	5.99E-04	9.24E-04	11	124453249	*SLC37A2*	Intron
rs7868264	6.00E-04	9.24E-04	9	137990431	*UBADC1*	Intron
rs4743641	6.00E-04	9.24E-04	9	105107354	*CYLC2*	Flanking_3UTR
rs1038335	6.02E-04	9.28E-04	6	2577107	*C6orf195*	Intron
rs2268084	6.03E-04	9.30E-04	20	32095049	*RALY*	Intron
rs319920	6.08E-04	9.37E-04	6	64562211	*PHF3*	Flanking_3UTR
rs330181	6.09E-04	9.37E-04	5	119059458	*LOC340069*	Flanking_3UTR
rs7432941	6.10E-04	9.39E-04	3	70345767	*MITF*	Flanking_3UTR
rs632374	6.10E-04	9.39E-04	11	96331679	*JRKL*	Flanking_3UTR
rs8137110	6.12E-04	9.42E-04	22	41141106	*NFAM1*	Intron
rs1696839	6.17E-04	9.49E-04	10	123499677	*ATE1*	Intron
rs9268832	6.20E-04	9.53E-04	6	32535767	*HLA-DRA*	Flanking_3UTR
rs1378624	6.20E-04	9.54E-04	2	196753322	*STK17B*	Flanking_5UTR
rs1529756	6.23E-04	9.58E-04	3	12976642	*IQSEC1*	Intron
rs7756268	6.30E-04	9.68E-04	6	51660261	*PKHD1*	Intron
rs2074565	6.32E-04	9.71E-04	14	68013900	*RAD51L1*	Intron
rs7553424	6.37E-04	9.79E-04	1	18232488	*IGSF21*	Flanking_5UTR
rs4075387	6.38E-04	9.80E-04	15	99297554	*ALDH1A3*	Flanking_3UTR
rs8018430	6.42E-04	9.85E-04	14	77727425	*NRXN3*	Flanking_5UTR
rs10943755	6.45E-04	9.90E-04	6	81653169	*BCKDHB*	Flanking_3UTR
rs2941503	6.46E-04	9.91E-04	17	35082271	*PERLD1*	3UTR
rs4837016	6.49E-04	9.96E-04	9	127181630	*GAPVD1*	Flanking_3UTR
rs13077437	6.50E-04	9.96E-04	3	24457322	*THRB*	Intron
rs1955850	6.50E-04	9.97E-04	14	26193254	*NOVA1*	Flanking_5UTR

UTR, Untranslated region.

TABLE E2. Association results of 37 imputed SNPs in *RAD50*

SNP	Position	*P* value	Location
rs12652920	131913139	1.36E-06	5′ Upstream
rs2057687	131915144	1.46E-02	5′ Upstream
rs2706338	131923748	9.98E-07	Intron 2
rs2244012	131929124	3.04E-07	Intron 2
rs2299015	131929396	9.98E-07	Intron 2
rs2706347	131933016	9.98E-07	Intron 2
rs2706348	131933709	9.98E-07	Intron 2
rs17166050	131943112	9.98E-07	Intron 4, near RHS3
rs2522403	131943216	9.98E-07	Intron 4, near RHS3
rs2246176	131945249	9.98E-07	Intron 5
rs2252775	131946343	9.98E-07	Intron 5
rs10463893	131955938	9.98E-07	Intron 11
rs2897443	131957493	2.74E-06	Intron 11
rs17622991	131960652	1.34E-06	Intron 13
rs2706370	131960915	1.65E-06	Intron 13
rs2706372	131963376	9.98E-07	Intron 13
rs6884762	131966629	9.23E-02	Intron 13
rs12187537	131967803	9.79E-07	Intron 15
rs2522394	131972028	9.79E-07	Intron 16
rs10520114	131976790	9.79E-07	Intron 19, near RHS4, LCR
rs2301713	131979895	1.49E-06	Intron 20, near RHS4, LCR
rs6596086	131980121	1.49E-06	Intron 20, near RHS4, LCR
rs2106984	131980965	1.49E-06	Intron 20, near RHS4, LCR
rs7449456	131981326	1.49E-06	Intron 20, near RHS4, LCR
rs17772583	131981409	2.28E-01	Intron 20, near RHS4, LCR
rs3798135	131993008	1.49E-06	Intron 21, on RHS5/LCR-O
rs3798134	131993078	1.49E-06	Intron 21, on RHS5/LCR-O
rs6596087	131996508	1.49E-06	Intron 21, LCR
rs6871536	131997773	9.03E-07	Intron 21, LCR
rs2237060	131998784	1.12E-01	Intron 21, near RHS6/ LCR-A
rs12653750	131999801	1.49E-06	Intron 21, on RHS6/LCR-A
rs2040703	132000157	1.34E-06	Intron 21, near RHS6/ LCR-A
rs2040704	132001076	1.33E-06	Intron 22, on RHS6/LCR-B
rs2074369	132001562	8.36E-07	Intron 22, LCR
rs7737470	132001962	1.94E-06	Intron 23, LCR
rs2240032	132005026	6.68E-06	Intron 24, on RHS7/LCR-C
rs2158177	132011957	1.48E-04	3′ Downstream

Boldface SNPs were genotyped SNPs; others were imputed.

TABLE E3. Forty-one association results of imputed SNPs in HLA-DR/DQ region ($P \leq 1.0E-04$)

SNP	Position	*P* value	Gene	Location
rs9268542	32492699	8.55E-05	*BTNL2*	Flanking_5UTR
rs9268544	32493431	8.55E-05	*BTNL2*	Flanking_5UTR
rs9268556	32494942	8.55E-05	*BTNL2*	Flanking_5UTR
rs9268644	32516022	6.55E-05	*HLA-DRA*	Intron
rs6926374	32517283	3.23E-05	*HLA-DRA*	Intron
rs9268657	32517634	6.54E-05	*HLA-DRA*	Intron
rs2239804	32519501	2.80E-05	*HLA-DRA*	Intron
rs2239803	32519811	2.80E-05	*HLA-DRA*	Intron
rs9268831	32535726	2.43E-05	*HLA-DRA*	Flanking_3UTR
rs9268853	32537621	7.30E-05	*HLA-DRA*	Flanking_3UTR
rs9268858	32537736	7.30E-05	*HLA-DRA*	Flanking_3UTR
rs2395185	32541145	1.00E-04	*HLA-DRA*	Flanking_3UTR
rs9405040	32547371	8.77E-05	*HLA-DRA*	Flanking_3UTR
rs9286790	32547806	8.77E-05	*HLA-DRA*	Flanking_3UTR
rs2516049	32678378	2.93E-05	*HLA-DRB1*	Flanking_5UTR
rs522308	32689900	4.34E-05	*HLA-DRB1*	Flanking_5UTR
rs3828800	32744041	4.34E-05	*HLA-DQB1*	Flanking_5UTR
rs9275184	32762692	1.26E-05	*HLA-DQB1*	Flanking_5UTR
rs9275207	32765688	5.10E-06	*HLA-DQB1*	Flanking_5UTR
rs9275221	32767077	5.10E-06	*HLA-DQB1*	Flanking_5UTR
rs9275293	32771286	5.10E-06	*HLA-DQB1*	Flanking_5UTR
rs5000634	32771542	9.76E-05	*HLA-DQB1*	Flanking_5UTR
rs7745040	32772310	3.23E-05	*HLA-DQB1*	Flanking_5UTR
rs9275307	32772968	2.68E-06	*HLA-DQB1*	Flanking_5UTR
rs9275310	32773297	4.72E-06	*HLA-DQB1*	Flanking_5UTR
rs9275311	32773618	4.72E-06	*HLA-DQB1*	Flanking_5UTR
rs9275312	32773706	1.13E-05	*HLA-DQB1*	Flanking_5UTR
rs9275313	32773737	5.95E-06	*HLA-DQB1*	Flanking_5UTR
rs9275319	32774273	1.28E-05	*HLA-DQB1*	Flanking_5UTR
rs9275324	32774613	4.72E-06	*HLA-DQB1*	Flanking_5UTR
rs9275328	32774800	1.24E-05	*HLA-DQB1*	Flanking_5UTR
rs9275330	32774853	1.12E-05	*HLA-DQB1*	Flanking_5UTR
rs9275334	32775085	2.68E-06	*HLA-DQB1*	Flanking_5UTR
rs9275338	32775321	1.13E-05	*HLA-DQB1*	Flanking_5UTR
rs9275351	32775771	2.68E-06	*HLA-DQB1*	Flanking_5UTR
rs9275356	32775828	2.68E-06	*HLA-DQB1*	Flanking_5UTR
rs9275592	32788598	2.68E-06	*HLA-DQA2*	Flanking_5UTR
rs7454108	32789461	2.68E-06	*HLA-DQA2*	Flanking_5UTR
rs3957146	32789508	2.68E-06	*HLA-DQA2*	Flanking_5UTR
rs3998159	32789997	1.45E-06	*HLA-DQA2*	Flanking_5UTR
rs9275599	32790407	2.96E-06	*HLA-DQA2*	Flanking_5UTR

BTNL2, Butyrophilin-like 2; *UTR*, Untranslated region.
Boldface SNPs were genotyped SNPs; others were imputed.