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Association analysis of SNPs in the IL4R locus with type I diabetes

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Abstract

The Type I Diabetes Genetics Consortium (T1DGC) has collected thousands of multiplex and simplex families with type I diabetes (T1D) with the goal of identifying genes involved in T1D susceptibility. These families have all been genotyped for the HLA class I and class II loci and a subset of samples has been typed for an major histocompatibility complex (MHC) single-nucleotide polymorphism (SNP) panel. In addition, the T1DGC has genotyped SNPs in candidate genes to evaluate earlier reported T1D associations. Individual SNPs and SNP haplotypes in IL4R, which encodes the α-chain of the IL4 and IL13 receptors, have been associated with T1D in some reports, but not in others. In this study, 38 SNPs in IL4R were genotyped using the Sequenom iPLEX Gold MassARRAY technology in 2042 multiplex families from nine cohorts. Association analyses (transmission-disequilibrium test and parental-disequilibrium test) were performed on individual SNPs and on three-SNP haplotypes. Analyses were also stratified on the high-risk HLA DR3/DR4-DQB1*0302 genotype. A modest T1D association in HBDI families (n = 282) was confirmed in this larger collection of HBDI families (n = 424). The variant alleles at the non-synonymous SNPs (rs1805011 (E400A), rs1805012 (C431R), and rs1801275 (Q576R)), which are in strong linkage disequilibrium, were negatively associated with T1D risk. These SNPs were more associated with T1D among non-DR3/DR4-DQB1*0302 genotypes than DR3/DR4-DQB1*0302 genotypes. This association was stronger, both in terms of odds ratio and P-values, than the initial report of the smaller collection of HBDI families. However, the IL4R SNPs and the three-SNP haplotype containing the variant alleles were not associated with T1D in the total data. Thus, in the overall families, these results do not show evidence for an association of SNPs in IL4R with T1D.

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Conflict of interest

The authors declare no conflict of interest.

Keywords

polymorphism; genotype; haplotype

Introduction

Type I diabetes (T1D), an autoimmune disease involving destruction of the insulin-producing cells of the pancreas, has a significant genetic component (λs = 15).[1] On the basis of linkage and association analyses, the strongest contribution (40–50%) comes from the HLA region.[2,3] Although alleles at the HLA-DR and -DQ-encoding loci are the major determinants of genetic risk for T1D,[4,5] association studies have revealed that multiple genes within the HLA region contribute to T1D risk.[6–12] In addition, many T1D susceptibility regions and genes outside the HLA region have been identified by linkage and by associations analyses.[13–15] Of the genes identified by association, some have been detected by hypothesis-free genome-wide approaches,[15] whereas others have been identified in candidate gene studies, on the basis of biological plausibility of the gene and/or of the specific polymorphism. Many of the candidate gene studies investigated a limited number of single-nucleotide polymorphisms (SNPs) and samples and, consequently, had very modest statistical power. The results of many of the reported candidate genes studies of T1D association are discordant. To address the issue of limited statistical power in the published candidate gene-association studies, the Type I Diabetes Genetics Consortium (T1DGC), an international collaboration that has collected thousands of multiplex and simplex T1D families,[16] has performed genotyping and association analysis of multiple SNPs in 21 T1D candidate genes.

One of the 21 candidate genes studied in the Rapid Response Project is *IL4R*, which encodes the α-chain of the IL4 and IL13 receptors. Polymorphisms in *IL4R* have been reported to be associated with allergy and asthma[17] and cervical cancer,[18] as well as with T1D;[19,20] several *IL4R* non-synonymous SNPs have been associated with differences in signaling.[21] A study of the multiplex HBDI families (n = 282) investigated eight SNPs in *IL4R* and, on the basis transmission–disequilibrium test (TDT) analysis, reported a modest protective effect of the variant allele at several tightly linked non-synonymous SNPs.[19] SNP rs1805015 (S503P) was the only individual SNP that exhibited nominal significance in this small study. This significance emerged only after stratification on families in which neither affected sib had the high-risk DR3/DR4-DQB1*0302 genotype. The percent transmission for the 503P variant allele was 44.6% (P = 0.06) for all families. In contrast, transmission of the 503P allele was 47.8% (P = 0.61) in families with a DR3/DR4-DQB1*0302-affected child and 42% (P = 0.03) in families in which neither affected sib had DR3/DR4-DQB1*0302. TDT analysis of an eight-SNP haplotype that included the variant alleles at rs1805011 (E400A), rs2234898 (L414L), rs1805012 (C431R), rs1805015 (S503P), and rs1801275 (Q576R) head a 33% transmission and an odds ratio (OR) of 0.49 (95% confidence interval (CI) = 0.28–0.81).

A small study of Filipino T1D cases and controls also reported an association of *IL4R* SNPs with T1D.[20] The association analysis in this study was performed without stratification on the DR3/DR4-DQB1*0302 genotype because this high-risk genotype is very rare in the Filipino population. Consistent with the earlier results,[19] this study reported a modest protective effect of a seven-SNP haplotype that included the same five variant alleles (400A 414L 431R, 503P, and 576R) (OR = 0.4; 95% CI = 0.2–0.8; P = 0.005). Four of the five SNPs are non-synonymous.

Two studies, one in Caucasian multiplex families and one in Filipino cases and controls, suggested that the variant alleles at a series of linked SNPs in *IL4R* were associated with protection from T1D. Small sample sizes and multiple testing, however, limited statistical

power. An earlier report found no association with *IL4R* (only rs1801275 and Q576R were genotyped).[22] More recently, a much larger study consisting of 3475 T1D families, including 1244 Finnish families, genotyped eight *IL4R* SNPs and found no significant evidence for association with T1D.[23] Subsequent to this report, another large study examined the *IL4R* SNPs and T1D in large family and case/control datasets and earlier published data and found no single-SNP association with T1D.[24]

In addition to the analysis of *IL4R* SNPs, the study of Filipino T1D cases and controls also investigated the possible association of SNPs in *IL4* and *IL13*, genes that encode the ligands of the IL4 receptor, and possible gene–gene interaction between SNPs in these genes and SNPs in *IL4R*. On the basis of the earlier small case–control data, risk for T1D might be determined by specific combinations of genotypes at *IL4R*, *IL4*, and *IL13*. However, the large study found no evidence for association or interaction between SNPs in *IL4R*, *IL4*, and *IL13*.[24]

The T1DGC carried out SNP genotyping on 38 SNPs in *IL4R*, 10 SNPs in *IL4*, and 5 SNPs in *IL13* on a collection of 2042 multiplex families from nine different populations. The data were subjected to TDT and parental TDT (PDT) analyses. An association analysis of the T1DGC genotyping data for 19 candidate genes, including the *IL4R*, *IL4*, and *IL13*, found no evidence of association for any of the SNPs in these three genes in the overall dataset.[25] Here, we present association analyses on the results from the individual cohorts in the *IL4R* T1DGC dataset.

Results

A panel of 38 SNPs in *IL4R* was genotyped using the Sequenom iPLEX platform on the nine cohorts (multiplex family collections from nine geographic locations) listed in Table 1. *IL4R* SNPs, their positions, and minor allele frequencies are shown in Table 2. Although 38 tagging SNPs in *IL4R* were attempted for genotyping in this study, two of the SNPS for which T1D associations were reported earlier, rs2234898 (L414L) and rs1805015 (S503P),[19] were not genotyped. The association analyses were performed using the TDT and PDT methods that used meiotic transmissions to each affected sib compared with expectation under the hypothesis of 'no association'. In addition, the analyses were stratified on the high-risk DR3/DR4-DQB1*0302 haplotype.

The patterns of LD among 38 *IL4R* SNPs are shown in Figure 1. None of the individual SNPs showed a statistically significant association with T1D in the overall dataset. All the *IL4R* SNPs that exhibited a nominally significant (<0.05) association with T1D by either TDT or PDT analysis in one or more of the different cohorts (before or after stratification) are shown in Table 3. No consistent pattern of association with T1D was observed across all cohorts.

A pattern of association consistent with the initial reports of T1D association was observed, however, in the HBDI cohort (Table 4).[19,20] The variant alleles for *IL4R* SNP rs1805011 (400A), rs1805012 (431R), and rs1801275 (576R) (a series of three linked non-synonymous SNPs) are associated with a reduced risk for T1D in the HBDI families, both in the absence of stratification and in those families with no DR3/DR4-DQB1*0302-affected siblings (Table 4). SNP rs1805011 (E400A) shows the strongest effect with a relative risk (RR) of 0.72 (95% CI = 0.57–0.9, $P = 0.0034$) in all HBDI families and an RR = 0.68 (0.51–0.92, $P = 0.010$) in the subset of families with no DR3-DR4-DQB1*0302-affected sibs.

The results of the analysis of three-marker haplotypes are provided in Table 5. A three-marker haplotype (consisting of the variant allele at rs1805011, rs1805012, and rs1801275) has a transmission of 41%, with an RR of 0.71, an OR of 0.54 (0.39–0.74), and a marginally significant TDT ($P = 0.043$) for this haplotype. The transmissions to each affected child in these multiplex families were all analyzed, so that the dataset is equivalent to 540 trio families with a DR3/DR4-DQB1*0302 and 342 trio families without a DR3/DR4-DQB1*0302-affected

child. This is in contrast to the initial study of 242 HBDI families in which transmission only to the proband was evaluated.[19] In addition, SNP rs3024537 also exhibited a modest protective effect in all HBDI families (RR = 0.79; 0.65–0.95) as well as in those without DR3/DR4-DQB1*0302 (RR = 0.77; CI 0.60–0.99) (Table 4). This SNP also was nominally protective in the North American and Asia-Pacific cohorts, but seemed to be positively associated with T1D in the Joslin cohort, although the sample size for this latter cohort was very small.

The strength of significance for the association of three-SNP haplotypes with T1D in the individual cohorts as well as the overall dataset is shown in Figure 2a–c. In the HBDI families, all three-SNP haplotypes containing the rs1805011 400A variant are associated with T1D in the unstratified analysis (Figure 2a); the haplotype with 400A as the middle SNP is also associated in the families without DR3/DR4-DQB1*0302 (Figure 2c). In the total data, haplotypes including the first three SNPs (rs2057768, rs2107356, and rs6498012) were associated in the unstratified data and in families with DR3/DR4-DQB1*0302. In these data, haplotypes with rs1805010 (I75V), rs2239347, rs3116578, and rs3024613 (all intronic) and rs4787426 and rs6498015 were associated in the unstratified data. Haplotypes with SNP rs4787426, rs12445135, rs4787427, rs7191188, and rs6498016 were also associated in the families with DR3/DR-DQB1*0302.

Discussion

Many published association studies of candidate gene polymorphisms examine only a few SNPs per gene and have relatively small sample sizes, resulting in limited statistical power to identify disease-associated alleles. Consequently, reports of association for candidate genes with T1D are often discordant. The extensive set of multiplex families, collected by the T1DGC, has enabled replication analyses of a variety of reported associations (the T1DGC Rapid Response Project). Although the association of three linked SNPs in *IL4R* observed in this large set of HBDI families was nominally significant and consistent with the initial reports in a subset of HBDI families and a small case/control study among Filipinos, no evidence for association of any individual SNPs was seen in the overall dataset.

The simplest interpretation of the lack of association of any of the individual *IL4R* SNPs in the overall data is that the earlier reported associations,[19,20] as well as the nominally significant observations within the HBDI cohort, are spurious and simply reflect false positive results (type I error). It may be premature, however, to definitively exclude *IL4R* as a T1D candidate gene. The HBDI families represent the largest individual cohort in the T1DGC dataset and the protective association of the three linked non-synonymous SNPs observed, after stratification, in the families without DR3/DR4-DQB1*0302 replicate earlier findings.[19] The set of HBDI families in the T1DGC collection include those studied in the initial report;[19] however, *two* meiotic transmissions, rather than *one* transmission per family, were analyzed in this larger T1DGC HBDI family collection. As a result, the association of *IL4R* SNPs with T1D became more significant with this expanded dataset. The question remains why *IL4R* SNPs seem to be associated in the HBDI cohort, but not in the overall dataset. It is conceivable that heterogeneity among these cohorts, in terms of environmental triggers or interacting genetic effects or linkage disequilibrium patterns, could account for these differences. Some three-SNP haplotypes show nominally significant association in the overall dataset, although, unlike rs180511 and flanking SNPs, there is no prior hypothesis associated with them. In conclusion, this large study of *IL4R* SNPs provides no clear and consistent evidence of T1D association, but the complex pattern of data suggests that some SNPs should not be definitively excluded as T1D-associated polymorphisms.

Materials and methods

Study population

The T1DGC has created a resource base of well-characterized families from multiple ethnic groups to characterization of T1D susceptibility genes (http://www.t1dgc.org). Genotyping for the Rapid Response project was performed on 2295 families in nine cohorts. The families selected for these analyses consisted mainly of nuclear families with an affected sib pair. This study reports the results for the *IL4R* gene in 9251 individuals, including 5580 children (4445 (80%) affected, 840 (15%) unaffected, and 295 (5%) unknown status) and 3671 parents (157 (4%) affected, 2576 (70%) unaffected, and 938 (26%) unknown status). The majority of the subjects were Caucasian (81%) with 18% unknown ethnicity and 1% other (Asian, African American, and Pacific Islander).

Genotyping

SNP genotyping was performed by the Broad Institute Center for Genotyping and Analysis (http://www.broad.mit.edu/gen_analysis/genotyping/). Aliquots of the T1DGC source 96-well plates were adjusted to 5–10 ng ml^{-1} in water in new 96-well plates. The iPLEX Gold chemistry of Sequenom's MassARRAY platform (San Diego, CA, USA) was used for genotyping of all SNPs as part of the larger set of T1DGC Rapid Response Project. Sequenom's SpectroDesigner software was used for SNP assay design, and SpectroTyper 4.0 was used to call genotypes automatically, followed by manual review.

Statistical genetic analysis

A TDT[26] was performed on each of the markers as implemented in Haploview software (version 4.1).[27] The transmission proportions were used to compute ORs and 95% CIs as described.28 The PDT method, as implemented in Haploview 4.1, was also used as a family based test of genetic association.29 This method incorporates parental phenotypes and, specifically, the parental genotype–phenotype correlation terms. The model is based on the between-within-sibship-association model using a liability-threshold-model approach. The incorporation of parental phenotypes can considerably increase power, as compared with the standard TDT and equivalent quantitative tests, whereas providing both significant protection against stratification and a means of evaluating the contribution of stratification to positive results. This methodology enables the extraction of more information from existing family based collections that are currently being genotyped and analyzed by use of standard approaches.

For pedigrees, full DRB1-DQB1 typing was available.[4] T1D patients were stratified into those carrying DR3/DR4, defined here as carrying one DRB1*0301-DQB1*0201 haplotype and one DRB1*0401/02/04/05/08-DQB1*0302/04 or DQB1*0201 haplotype. All other participants were categorized as non-DR3/DR4.

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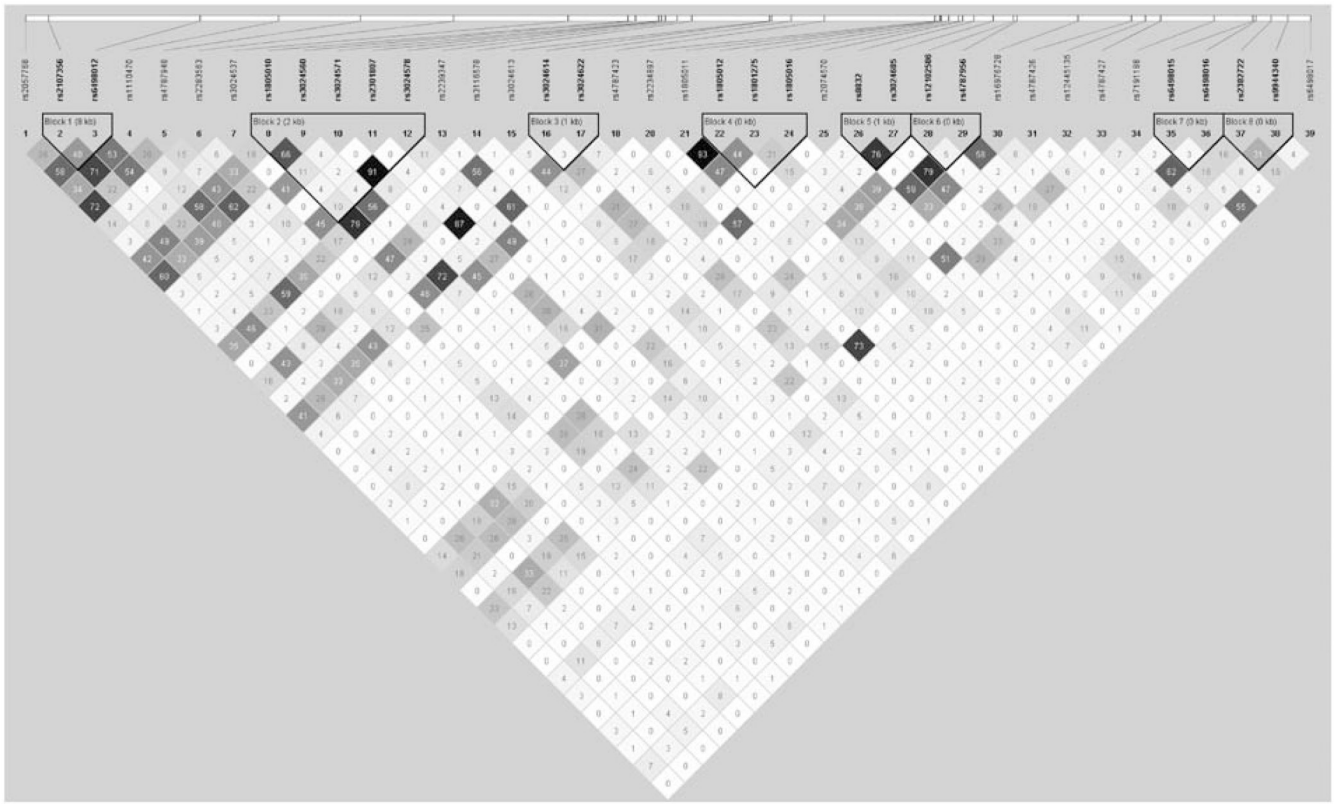

Figure 1.
Linkage disequilibrium (R^2) values between all SNPs across all cohorts.

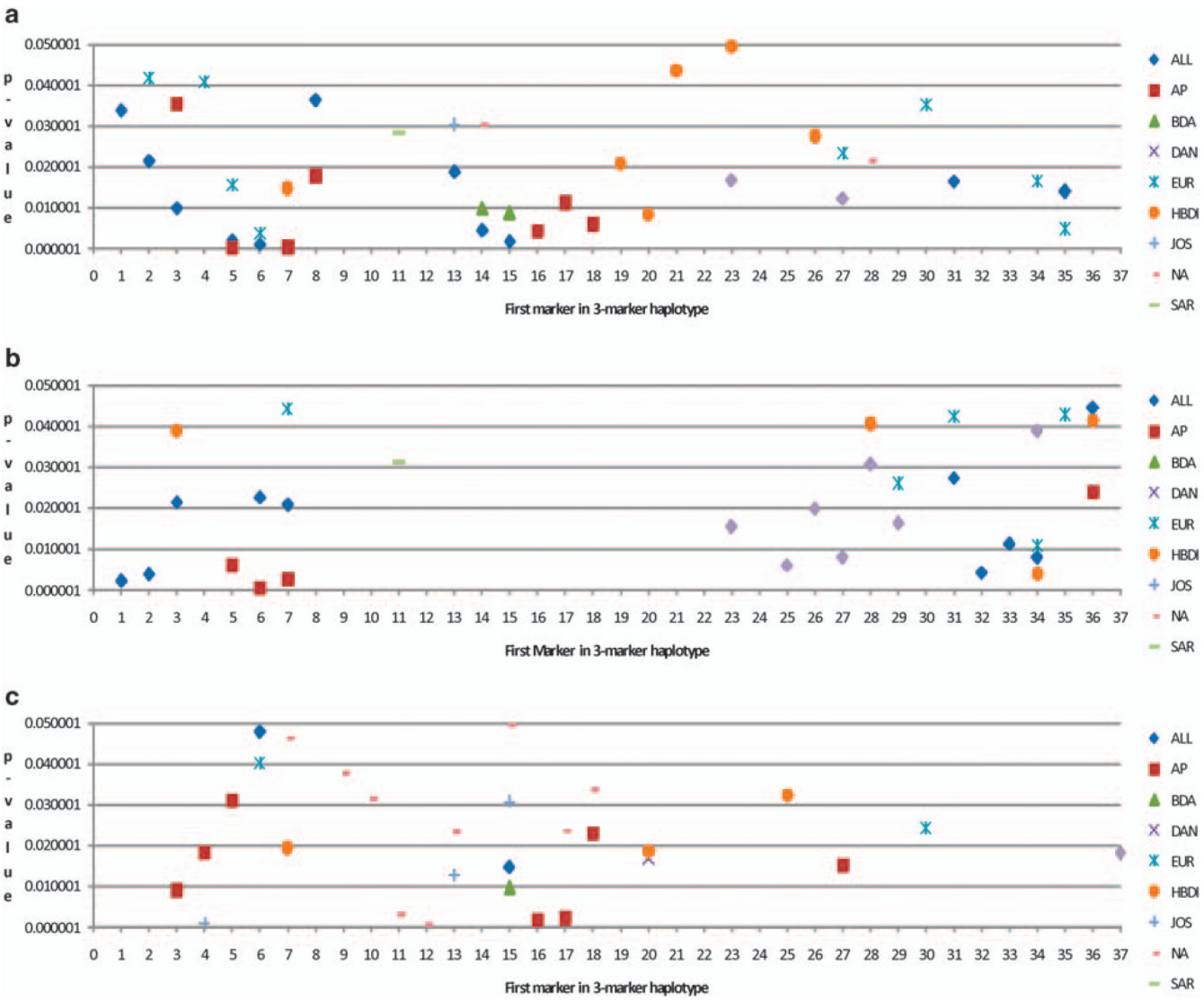

Figure 2.

TDT significance in *IL4R* three-SNP haplotypes: (**a**) TDT significance in three locus haplotypes, no stratification; (**b**) TDT significance in three locus haplotypes with DR3/DR4-DQB1*0302; and (**c**) TDT significance in three locus haplotypes without DR3/DR4-DQB1*0302.

Table 1

Cohorts used for the study (proportions of DR3/DR4 vs non-DR3/DR4 are shown, as well as average age of onset in each cohort)

Region	Cohort	N pedigrees	N pedigrees MHC	Not DR3/DR4 trios	DR3/DR4 trios	Age of onset mean	s.d.	n T1D patients age of onset	Num peds with age of onset
1	AP	169	118	130	109	10.34	7.94	366	169
2	DAN	130	94	106	85	14.99	11.23	293	130
2	EUR	428	329	429	232	11.83	8.26	893	428
4	HBDI	424	413	540	342	12.28	8.67	937	415
4	JOS	71	53	56	52	11.83	7.53	148	71
4	NA	295	217	263	172	8.76	6.62	637	295
5	BDA	393	0	0	0	12.60	9.76	853	391
5	SAR	74	52	51	52	12.75	8.71	150	74
5	UK	108	91	93	90	8.22	5.29	242	108
	Total	2092	1367	1668	1134				

Abbreviations: MHC, major histocompatibility complex; T1D, type I diabetes.

Table 2

IL4R SNPs tested, their locations, alleles, and functions

Marker number	SNP ID	Reference assembly chromosome position	Major allele	Minor allele	Minor allele frequency	SNP function[a]
1	rs2057768	27229596	C	T	0.2874	Not reported[b]
2	rs2107356	27230905	G	A	0.4125	5′ near gene
3	rs6498012	27239475	C	G	0.379	Intron
4	rs1110470	27243928	C	T	0.4733	Intron
5	rs4787948	27248560	A	G	0.2933	Intron
6	rs2283563	27253855	G	A	0.3121	Intron
7	rs3024537	27260320	G	A	0.1438	Intron
8	rs1805010	27263704	A	G	0.4466	I75V
9	rs3024560	27264168	T	G	0.3536	Intron
10	rs3024571	27265428	C	T	0.0891	N167N
11	rs2301807	27265599	G	T	0.0499	Intron
12	rs3024578	27265852	G	A	0.0826	Intron
13	rs2239347	27266522	A	C	0.4548	Intron
14	rs3116578	27267337	C	T	0.0201	Intron
15	rs3024613	27271754	G	A	0.4816	Intron
16	rs3024614	27271846	A	G	0.0562	Intron
17	rs3024622	27272954	C	G	0.3448	Intron
18	rs4787423	27274835	T	C	0.1368	Intron
19	rs3024668	27279450	C	T	0.0524	Intron
20	rs2234897	27281113	T	C	0.0244	F313F
21	rs1805011	27281373	A	C	0.1137	E400A
22	rs1805012	27281465	T	C	0.1053	C431R
23	rs1801275	27281901	A	G	0.2114	Q576R
24	rs1805016	27282428	A	C	0.0558	S752A
25	rs2074570	27282658	A	G	0.0405	3′ UTR
26	rs8832	27283288	G	A	0.4423	3′ UTR
27	rs3024685	27284411	A	G	0.3923	Not reported[b]
28	rs12102586	27285554	C	T	0.0914	Not reported[b]

Marker number	SNP ID	Reference assembly chromosome position	Major allele	Minor allele	Minor allele frequency	SNP function[a]
29	rs4787956	27285750	T	C	0.3439	Not reported[b]
30	rs16976728	27289213	G	A	0.3831	Not reported[b]
31	rs4787426	27292232	T	G	0.1271	Not reported[b]
32	rs12445135	27293007	C	T	0.0298	Not reported[b]
33	rs4787427	27293895	C	G	0.324	Not reported[b]
34	rs7191188	27296912	C	T	0.2386	Not reported[b]
35	rs6498015	27299125	C	T	0.1287	Not reported[b]
36	rs6498016	27299289	G	A	0.1842	Not reported[b]
37	rs2382722	27300127	A	G	0.4611	Not reported[b]
38	rs9944340	27301092	T	C	0.2699	Not reported[b]
39	rs6498017	27302359	G	A	0.1396	Not reported[b]

[a] Single-nucleotide polymorphism (SNP) location relative to the *IL4R* gene and function in the context of changes to the peptide sequence of the *IL4R* gene, as described in the GeneView 'Function' entries of the relevant entry for each rs number in the NCBI's Entrez dbSNP database.

[b] No data was available in the GeneView entry describing this SNP as resulting in either a synonymous or non-synonymous replacement, or describing a change in an untranslated region as being in a 5′ UTR, 3′ UTR, or intron.

Table 3

RR in *IL4R* SNPs with significant TDT or PDT *P*-values

Cohort	Stratification	Marker number	SNP	Over-transmitted allele	IS	TU	% Trans	TDT *P*-value	PDT *P*-value	RR minor	CI_minor
EUR	DR3/DR4-DQB1*0302+	1	rs2057768	C	Major	110:82	0.5729	**0.0429**	0.2782	0.75	(0.56–0.99)
EUR	No stratification	1	rs2057768	C	Major	244:198	0.5520	**0.0285**	**0.0365**	0.81	(0.67–0.98)
EUR	DR3/DR4-DQB1*0302+	2	rs2107356	A	Minor	154:118	0.5662	**0.0288**	0.0652	1.31	(0.60–0.97)
EUR	No stratification	2	rs2107356	A	Minor	361:300	0.5461	**0.0176**	**0.0186**	1.20	(0.71–0.97)
NA	DR3/DR4-DQB1*0302−	2	rs2107356	A	Minor	123:92	0.5721	**0.0342**	**0.0204**	1.34	(0.57–0.98)
SAR	No stratification	2	rs2107356	G	Major	66:44	0.6000	**0.0353**	0.0972	0.67	(0.45–0.98)
EUR	DR3/DR4-DQB1*0302+	3	rs6498012	C	Major	136:102	0.5714	**0.0273**	0.0975	0.75	(0.58–0.97)
EUR	No stratification	3	rs6498012	C	Major	304:245	0.5537	**0.0117**	**0.0158**	0.81	(0.68–0.95)
EUR	No stratification	4	rs1110470	T	Minor	325:277	0.5399	0.0503	**0.0285**	1.17	(1.00–1.38)
SAR	No stratification	4	rs1110470	C	Major	71:48	0.5966	**0.0344**	0.0985	0.68	(0.47–0.97)
AP	DR3/DR4-DQB1*0302−	5	rs4787948	A	Major	54:29	0.6506	**0.0057**	0.0851	0.54	(0.34–0.84)
AP	No stratification	5	rs4787948	A	Major	106:65	0.6199	**0.0016**	0.2415	0.61	(0.45–0.83)
DAN	DR3/DR4-DQB1*0302−	5	rs4787948	A	Major	29:23	0.5577	0.4049	**0.0411**	0.79	(0.46–1.37)
NA	DR3/DR4-DQB1*0302−	6	rs2283563	A	Minor	104:72	0.5909	**0.0156**	**0.0010**	1.44	(0.51–0.93)
NA	No stratification	6	rs2283563	A	Minor	159:130	0.5502	0.0878	**0.0017**	1.22	(0.65–1.03)
AP	DR3/DR4-DQB1*0302−	7	rs3024537	G	Major	35:13	0.7292	**0.0012**	0.3410	0.37	(0.20–0.70)
AP	DR3/DR4-DQB1*0302+	7	rs3024537	G	Major	47:16	0.7460	**0.0001**	**0.0006**	0.34	(0.19–0.60)
AP	No stratification	7	rs3024537	G	Major	82:29	0.7387	**0.0000**	**0.0009**	0.35	(0.23–0.54)
HBDI	DR3/DR4-DQB1*0302−	7	rs3024537	G	Major	134:103	0.5654	**0.0437**	**0.0274**	0.77	(0.60–0.99)
HBDI	No stratification	7	rs3024537	G	Major	239:188	0.5597	**0.0135**	**0.0088**	0.79	(0.65–0.95)
JOS	DR3/DR4-DQB1*0302+	7	rs3024537	A	Minor	17:7	0.7083	**0.0382**	0.0772	2.43	(0.17–0.99)
NA	DR3/DR4-DQB1*0302−	7	rs3024537	G	Major	51:31	0.6220	**0.0264**	0.1452	0.61	(0.39–0.95)
BDA	DR3/DR4-DQB1*0302−	8	rs1805010	G	Minor	169:132	0.5615	**0.0327**	0.1089	1.28	(1.02–1.61)
JOS	DR3/DR4-DQB1*0302−	8	rs1805010	A	Major	23:13	0.6389	0.0934	**0.0254**	0.56	(0.29–1.11)
NA	DR3/DR4-DQB1*0302−	8	rs1805010	A	Major	115:81	0.5867	**0.0149**	**0.0166**	0.70	(0.53–0.93)
EUR	DR3/DR4-DQB1*0302+	9	rs3024560	T	Major	130:100	0.5652	**0.0476**	0.2078	0.77	(0.59–1.00)
NA	DR3/DR4-DQB1*0302−	10	rs3024571	C	Major	40:20	0.6667	**0.0091**	**0.0327**	0.50	(0.29–0.85)
NA	No stratification	10	rs3024571	C	Major	71:48	0.5966	**0.0344**	**0.0416**	0.68	(0.47–0.97)

Cohort	Stratification	Marker number	SNP	Over-transmitted allele	IS	TU	% Trans	TDT *P*-value	PDT *P*-value	RR minor	CI_minor
NA	DR3/DR4-DQB1*0302−	12	rs3024578	G	Major	36:18	0.6667	**0.0134**	0.0631	0.50	(0.28–0.88)
JOS	DR3/DR4-DQB1*0302−	13	rs2239347	A	Major	20:12	0.6250	0.1551	**0.0455**	0.60	(0.29–1.23)
NA	DR3/DR4-DQB1*0302−	13	rs2239347	A	Major	129:83	0.6085	**0.0015**	**0.0017**	0.65	(0.49–0.85)
BDA	DR3/DR4-DQB1*0302−	15	rs3024613	G	Major	163:125	0.5660	**0.0249**	**0.0396**	0.77	(0.61–0.97)
BDA	No stratification	15	rs3024613	G	Major	304:253	0.5458	**0.0306**	0.0614	0.83	(0.70–0.98)
DAN	DR3/DR4-DQB1*0302−	15	rs3024613	A	Minor	43:29	0.5972	0.0979	**0.0483**	1.48	(0.42–1.08)
AP	DR3/DR4-DQB1*0302−	17	rs3024622	G	Minor	64:43	0.5981	**0.0417**	**0.0189**	1.49	(1.01–2.19)
EUR	DR3/DR4-DQB1*0302+	17	rs3024622	C	Major	131:101	0.5647	**0.0486**	0.1021	0.77	(0.60–1.00)
AP	No stratification	18	rs4787423	T	Major	64:37	0.6337	**0.0069**	0.0977	0.58	(0.39–0.87)
DAN	DR3/DR4-DQB1*0302−	20	rs2234897	T	Major	4:0	1.0000	**0.0185**	0.0578	0.11	(0.01–2.08)
AP	DR3/DR4-DQB1*0302−	21	rs1805011	C	Minor	30:16	0.6522	**0.0375**	0.0587	1.88	(1.02–3.44)
HBDI	DR3/DR4-DQB1*0302−	21	rs1805011	A	Major	111:76	0.5936	**0.0103**	**0.0153**	0.68	(0.51–0.92)
HBDI	No stratification	21	rs1805011	A	Major	184:132	0.5823	**0.0034**	**0.0071**	0.72	(0.57–0.90)
HBDI	DR3/DR4-DQB1*0302−	22	rs1805012	T	Major	112:79	0.5864	**0.0167**	**0.0208**	0.70	(0.53–0.94)
HBDI	No stratification	22	rs1805012	T	Major	183:133	0.5791	**0.0048**	**0.0094**	0.72	(0.58–0.91)
AP	DR3/DR4-DQB1*0302−	23	rs1801275	G	Minor	47:27	0.6351	**0.0193**	**0.0239**	1.74	(1.08–2.79)
DAN	DR3/DR4-DQB1*0302+	23	rs1801275	G	Minor	38:22	0.6333	**0.0377**	**0.0104**	1.73	(1.02–2.92)
HBDI	DR3/DR4-DQB1*0302−	23	rs1801275	A	Major	169:133	0.5596	**0.0381**	**0.0309**	0.79	(0.63–0.99)
HBDI	No stratification	23	rs1801275	A	Major	287:238	0.5467	**0.0323**	**0.0338**	0.83	(0.7–0.98)
AP	DR3/DR4-DQB1*0302−	24	rs1805016	A	Major	8:4	0.6667	0.2437	**0.0285**	0.50	(0.15–1.67)
DAN	DR3/DR4-DQB1*0302+	24	rs1805016	C	Minor	15:6	0.7143	**0.0459**	**0.0311**	2.50	(0.97–6.44)
DAN	No stratification	24	rs1805016	C	Minor	28:16	0.6364	0.0687	**0.0222**	1.75	(0.95–3.23)
JOS	DR3/DR4-DQB1*0302−	24	rs1805016	C	Minor	3:0	1.0000	**0.0414**	0.1573	7.00	(0.36–135.52)
DAN	DR3/DR4-DQB1*0302−	25	rs2074570	A	Major	8:2	0.8000	**0.0496**	0.1167	0.25	(0.05–1.18)
UK	DR3/DR4-DQB1*0302+	25	rs2074570	A	Major	14:4	0.7778	**0.0153**	**0.0222**	0.29	(0.09–0.87)
UK	No stratification	25	rs2074570	A	Major	22:9	0.7097	**0.0177**	**0.0097**	0.41	(0.19–0.88)
UK	DR3/DR4-DQB1*0302+	27	rs3024685	G	Minor	60:40	0.6000	**0.0448**	0.1365	1.50	(1.01–2.24)
DAN	DR3/DR4-DQB1*0302+	28	rs12102586	T	Minor	27:11	0.7105	**0.0084**	**0.0040**	2.45	(1.22–4.95)
SAR	DR3/DR4-DQB1*0302−	28	rs12102586	T	Minor	6:1	0.8571	**0.0465**	0.2059	6.00	(0.72–49.84)
UK	No stratification	28	rs12102586	C	Major	41:23	0.6406	**0.0235**	**0.0378**	0.56	(0.34–0.93)
EUR	DR3/DR4-DQB1*0302+	29	rs4787956	T	Major	117:86	0.5764	**0.0293**	0.0617	0.74	(0.56–0.97)

Cohort	Stratification	Marker number	SNP	Over-transmitted allele	IS	TU	% Trans	TDT *P*-value	PDT *P*-value	RR minor	CI_minor
EUR	No stratification	29	rs4787956	T	Major	280:237	0.5416	0.0585	**0.0465**	0.85	(0.71–1.01)
UK	DR3/DR4-DQB1*0302+	29	rs4787956	C	Minor	57:34	0.6264	**0.0153**	**0.0489**	1.68	(0.39–0.91)
UK	DR3/DR4-DQB1*0302+	30	rs16976728	A	Minor	55:36	0.6044	**0.0456**	0.1181	1.53	(0.43–1.00)
EUR	DR3/DR4-DQB1*0302+	31	rs4787426	T	Major	61:40	0.6040	**0.0360**	0.2243	0.66	(0.44–0.98)
EUR	No stratification	31	rs4787426	T	Major	147:112	0.5676	**0.0294**	0.0868	0.76	(0.60–0.97)
DAN	DR3/DR4-DQB1*0302−	32	rs12445135	C	Major	6:0	1.0000	**0.0039**	**0.0348**	0.08	(0.004–1.37)
JOS	No stratification	32	rs12445135	T	Minor	6:1	0.8571	**0.0465**	0.0833	6.00	(0.72–49.84)
UK	DR3/DR4-DQB1*0302−	33	rs4787427	G	Minor	32:17	0.6531	**0.0308**	**0.0469**	1.88	(1.05–3.39)
UK	DR3/DR4-DQB1*0302−	34	rs7191188	C	Major	38:22	0.6333	**0.0377**	0.0652	0.58	(0.34–0.98)
EUR	DR3/DR4-DQB1*0302−	35	rs6498015	C	Major	100:65	0.6061	**0.0062**	0.2798	0.65	(0.48–0.88)
EUR	No stratification	35	rs6498015	C	Major	148:107	0.5804	**0.0101**	0.2535	0.72	(0.56–0.93)
UK	DR3/DR4-DQB1*0302−	35	rs6498015	T	Minor	27:14	0.6585	**0.0406**	**0.0478**	1.93	(1.01–3.68)
UK	No stratification	35	rs6498015	T	Minor	51:32	0.6145	**0.0362**	0.0637	1.59	(1.02–2.48)
EUR	DR3/DR4-DQB1*0302−	36	rs6498016	A	Minor	127:96	0.5695	**0.0376**	**0.0148**	1.32	(0.58–0.99)
EUR	No stratification	36	rs6498016	A	Minor	201:150	0.5726	**0.0064**	**0.0070**	1.34	(0.60–0.92)
SAR	DR3/DR4-DQB1*0302−	36	rs6498016	G	Major	17:7	0.7083	**0.0382**	0.0643	0.41	(0.17–0.99)
UK	DR3/DR4-DQB1*0302−	36	rs6498016	G	Major	34:18	0.6538	**0.0253**	**0.0388**	0.53	(0.30–0.93)
HBDI	No stratification	37	rs2382722	A	Major	386:345	0.5280	0.1293	**0.0492**	0.89	(0.78–1.03)
UK	DR3/DR4-DQB1*0302−	37	rs2382722	G	Minor	38:21	0.6441	**0.0258**	**0.0182**	1.81	(1.06–3.08)
AP	DR3/DR4-DQB1*0302+	38	rs9944340	T	Major	56:29	0.6588	**0.0031**	**0.0172**	0.52	(0.33–0.81)
EUR	DR3/DR4-DQB1*0302+	38	rs9944340	T	Major	109:77	0.5860	**0.0187**	**0.0074**	0.70	(0.53–0.94)

Abbreviations: CI, confidence interval; PDT, parental-disequilibrium test; RR, relative risk; SNP, single-nucleotide polymorphism; TDT, transmission-disequilibrium test.

Significant *P*-values are shown in bold.

Table 4

RR in *IL4R* SNPs with significant TDT or PDT *P*-values in the HBDI families

Cohort	Stratification	Marker number	SNP	Over-transmitted allele	IS	TU	% Trans	TDT *P*-value	PDT *P*-value	RR minor	CI_minor
HBDI	DR3/DR4-DQB1*0302−	7	rs3024537	G	Major	134:103	0.5654	**0.0437**	**0.0274**	0.77	(0.60–0.99)
HBDI	No stratification	7	rs3024537	G	Major	239:188	0.5597	**0.0135**	**0.0088**	0.79	(0.65–0.95)
HBDI	DR3/DR4-DQB1*0302−	21	rs1805011	A	Major	111:76	0.5936	**0.0103**	**0.0153**	0.68	(0.51–0.92)
HBDI	No stratification	21	rs1805011	A	Major	184:132	0.5823	**0.0034**	**0.0071**	0.72	(0.57–0.90)
HBDI	DR3/DR4-DQB1*0302−	22	rs1805012	T	Major	112:79	0.5864	**0.0167**	**0.0208**	0.70	(0.53–0.94)
HBDI	No stratification	22	rs1805012	T	Major	183:133	0.5791	**0.0048**	**0.0094**	0.72	(0.58–0.91)
HBDI	DR3/DR4-DQB1*0302−	23	rs1801275	A	Major	169:133	0.5596	**0.0381**	**0.0309**	0.79	(0.63–0.99)
HBDI	No stratification	23	rs1801275	A	Major	287:238	0.5467	**0.0323**	**0.0338**	0.83	(0.70–0.98)
HBDI	No stratification	37	rs2382722	A	Major	386:345	0.5280	0.1293	**0.0492**	0.89	(0.78–1.03)

Abbreviations: CI, confidence interval; PDT, parental-disequilibrium test; RR, relative risk; SNP, single-nucleotide polymorphism; TDT, transmission-disequilibrium test.

Significant *P*-values are shown in bold.

Table 5

Significant three-locus haplotypes in the HBDI families

Marker numbers	SNP 1	SNP 2	SNP 3	Stratification	TDT *P*-value	Haplotype	Number transmitted	Number not transmitted	% Transmitted	RR	OR	OR CI
3-4-5	rs6498012	rs1110470	rs4787948	DR3/DR4-DQB1*0302+	0.039	C-T-A	120	94	56.07	1.23	1	1–1
	rs6498012	rs1110470	rs4787948		0.039	G-C-G	92	88	51.11	1.19	0.82	0.55–1.22
	rs6498012	rs1110470	rs4787948		0.039	C-C-A	60	71	45.79	1.00	0.66	0.43–1.02
	rs6498012	rs1110470	rs4787948		0.039	G-C-A	25	42	37.32	0.65	0.47	0.27–0.82
	rs6498012	rs1110470	rs4787948		0.039	C-T-G	0	2	0.00	2.00E-08	0	0–0
7–8–9	rs3024537	rs1805010	rs3024560	None	0.014	G-G-G	251	232	51.96	1.73	0.95	0.74–1.22
	rs3024537	rs1805010	rs3024560		0.014	G-A-T	290	255	53.21	1.72	1	1–1
	rs3024537	rs1805010	rs3024560		0.014	A-G-T	91	98	48.15	1.57	0.82	0.59–1.14
	rs3024537	rs1805010	rs3024560		0.014	G-G-T	18	21	46.15	1.42	0.75	0.39–1.45
	rs3024537	rs1805010	rs3024560		0.014	A-G-G	55	99	35.72	1.00	0.49	0.34–0.71
7-8-9	rs3024537	rs1805010	rs3024560	DR3/DR4-DQB1*0302−	0.019	A-G-T	52	48	52.01	2.07	0.99	0.63–1.55
	rs3024537	rs1805010	rs3024560		0.019	G-G-G	149	130	53.40	2.01	1.05	0.76–1.45
	rs3024537	rs1805010	rs3024560		0.019	G-A-T	161	147	52.27	1.91	1	1–1
	rs3024537	rs1805010	rs3024560		0.019	G-G-T	9	12	42.86	1.41	0.68	0.28–1.67
	rs3024537	rs1805010	rs3024560		0.019	A-G-G	31	65	32.29	1.00	0.44	0.27–0.71
19-20-21	rs3024668	rs2234897	rs1805011	None	0.021	C-T-A	203	142	58.84	1.11	1	1–1
	rs3024668	rs2234897	rs1805011		0.021	C-C-A	24	26	48.00	1.00	0.65	0.36–1.17
	rs3024668	rs2234897	rs1805011		0.021	T-T-C	56	70	44.44	0.88	0.56	0.37–0.84
	rs3024668	rs2234897	rs1805011		0.021	C-T-C	*77*	117	39.69	0.74	0.46	0.32–0.66
	rs3024668	rs2234897	rs1805011		0.021	T-T-A	4	9	30.77	0.51	0.31	0.09–1.03
20-21-22	rs2234897	rs1805011	rs1805012	None	0.008	T-A-T	193	135	58.84	1.16	1	1–1
	rs2234897	rs1805011	rs1805012		0.008	C-A-T	23	26	46.94	1.00	0.62	0.34–1.13
	rs2234897	rs1805011	rs1805012		0.008	T-C-C	118	168	41.26	0.83	0.49	0.36–0.68
	rs2234897	rs1805011	rs1805012		0.008	T-C-T	2	7	22.22	0.29	0.20	0.04–0.98
20-21-22	rs2234897	rs1805011	rs1805012	DR3/DR4-DQB1*0302−	0.019	T-A-T	116	75	60.73	1.30	1	1–1
	rs2234897	rs1805011	rs1805012		0.019	C-A-T	13	16	44.83	1.00	0.53	0.24–1.15
	rs2234897	rs1805011	rs1805012		0.019	T-C-C	68	101	40.24	0.88	0.44	0.29–0.66
	rs2234897	rs1805011	rs1805012		0.019	T-C-T	2	7	22.22	0.32	0.18	0.04–0.91

Marker numbers	SNP 1	SNP 2	SNP 3	Stratification	TDT *P*-value	Haplotype	Number transmitted	Number not transmitted	% Transmitted	RR	OR	OR CI
21-22-23	rs1805011	rs1805012	rs1801275	None	0.043	A-T-A	231	181	56.07	1.00	1	1–1
	rs1805011	rs1805012	rs1801275		0.043	A-T-G	94	97	49.21	0.97	0.76	0.54–1.07
	rs1805011	rs1805012	rs1801275		0.043	C-C-G	103	149	40.87	0.71	0.54	0.39–0.74
	rs1805011	rs1805012	rs1801275		0.043	C-T-G	2	3	40.00	0.54	0.52	0.09–3.16
23–24–25	rs1801275	rs1805016	rs2074570	None	0.049	G-C-G	2	0	100.00	77740	Inf	0–infinity
	rs1801275	rs1805016	rs2074570		0.049	A-A-A	237	190	55.50	1.00	1	1–1
	rs1801275	rs1805016	rs2074570		0.049	G-C-A	65	65	50.00	0.98	0.80	0.54–1.19
	rs1801275	rs1805016	rs2074570		0.049	G-A-G	34	36	48.57	0.98	0.76	0.46–1.26
	rs1801275	rs1805016	rs2074570		0.049	G-A-A	114	161	41.45	0.74	0.57	0.42–0.77
25-26-27	rs2074570	rs8832	rs3024685	DR3/DR4-DQB1*0302−	0.032	A-G-G	6	4	59.99	2.89	1.19	0.33–4.31
	rs2074570	rs8832	rs3024685		0.032	G-A-G	2	2	50.00	2.12	0.80	0.11–5.72
	rs2074570	rs8832	rs3024685		0.032	A-G-A	191	152	55.68	2.12	1	1–1
	rs2074570	rs8832	rs3024685		0.032	A-A-G	152	159	48.88	1.88	0.76	0.56–1.04
	rs2074570	rs8832	rs3024685		0.032	G-G-A	21	25	45.65	1.64	0.67	0.36–1.24
	rs2074570	rs8832	rs3024685		0.032	A-A-A	27	57	32.14	1.00	0.38	0.23–0.62
26-27-28	rs8832	rs3024685	rs12102586	None	0.027	G-G-C	13	8	61.91	2.57	1.42	0.58–3.47
	rs8832	rs3024685	rs12102586		0.027	A-G-T	56	43	56.57	1.99	1.14	0.74–1.74
	rs8832	rs3024685	rs12102586		0.027	G-A-C	327	285	53.43	1.62	1	1–1
	rs8832	rs3024685	rs12102586		0.027	A-G-C	257	273	48.49	1.48	0.82	0.65–1.04
	rs8832	rs3024685	rs12102586		0.027	G-A-T	45	55	45.00	1.25	0.71	0.47–1.09
	rs8832	rs3024685	rs12102586		0.027	A-A-C	55	89	38.19	1.00	0.54	0.37–0.78
26-27-28	rs8832	rs3024685	rs12102586	DR3/DR4-DQB1*0302−	0.020	G-G-C	6	4	60.00	2.87	1.15	0.32–4.15
	rs8832	rs3024685	rs12102586		0.020	A-G-T	33	25	56.90	2.40	1.01	0.58–1.78
	rs8832	rs3024685	rs12102586		0.020	G-A-C	188	144	56.63	2.08	1	1–1
	rs8832	rs3024685	rs12102586		0.020	A-G-C	143	164	46.59	1.74	0.67	0.49–0.91
	rs8832	rs3024685	rs12102586		0.020	G-A-T	25	32	43.86	1.42	0.60	0.34–1.05
	rs8832	rs3024685	rs12102586		0.020	A-A-C	26	52	33.34	1.00	0.38	0.23–0.64
28-29-30	rs12102586	rs4787956	rs16976728	DR3/DR4-DQB1*0302+	0.041	C-C-A	121	87	58.17	1.00	1.49	1.04–2.14
	rs12102586	rs4787956	rs16976728		0.041	C-T-G	135	145	48.21	0.78	1	1–1
	rs12102586	rs4787956	rs16976728		0.041	T-T-A	7	8	46.66	0.71	0.94	0.33–2.66
	rs12102586	rs4787956	rs16976728		0.041	T-T-G	31	37	45.59	0.68	0.90	0.53–1.53

Marker numbers	SNP 1	SNP 2	SNP 3	Stratification	TDT *P*-value	Haplotype	Number transmitted	Number not transmitted	% Transmitted	RR	OR	OR CI
	rs12102586	rs4787956	rs16976728		0.041	C-T-A	37	42	46.84	0.67	0.95	0.57–1.56
	rs12102586	rs4787956	rs16976728		0.041	C-C-G	6	18	25.00	0.25	0.36	0.14–0.93
34-35-36	rs7191188	rs6498015	rs6498016	DR3/DR4-DQB1*0302+	0.004	C-C-A	12	5	70.59	1.00	2.87	0.98–8.37
	rs7191188	rs6498015	rs6498016		0.004	C-T-G	63	48	56.75	0.62	1.57	1–2.45
	rs7191188	rs6498015	rs6498016		0.004	T-C-A	79	70	53.02	0.53	1.35	0.9–2.02
	rs7191188	rs6498015	rs6498016		0.004	T-C-G	29	28	50.88	0.50	1.24	0.7–2.2
	rs7191188	rs6498015	rs6498016		0.004	C-C-G	118	141	45.56	0.45	1	1–1
	rs7191188	rs6498015	rs6498016		0.004	T-T-G	0	9	0.00	5.16E-10	0	0–0
36-37-38	rs6498016	rs2382722	rs9944340	DR3/DR4-DQB1*0302+	0.041	G-G-C	2	0	1.00	1.33E+09	Inf	0–infinity
	rs6498016	rs2382722	rs9944340		0.041	G-A-T	48	37	56.48	1.04	1.59	0.96–2.62
	rs6498016	rs2382722	rs9944340		0.041	A-A-T	84	65	56.37	1.00	1.58	1.04–2.4
	rs6498016	rs2382722	rs9944340		0.041	G-A-C	90	96	48.38	0.79	1.15	0.78–1.69
	rs6498016	rs2382722	rs9944340		0.041	G-G-T	103	126	44.98	0.74	1	1–1
	rs6498016	rs2382722	rs9944340		0.041	A-G-T	0	3	0.00	2.05E-08	0	0–0

Abbreviations: OR, odds ratio; RR, relative risk; SNP, single-nucleotide polymorphism; TDT, transmission-disequilibrium test.