

## EXTENDED REPORT

# Comprehensive assessment of rheumatoid arthritis susceptibility loci in a large psoriatic arthritis cohort

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## ABSTRACT

**Objective** A number of rheumatoid arthritis (RA) susceptibility genes have been identified in recent years. Given the overlap in phenotypic expression of synovial joint inflammation between RA and psoriatic arthritis (PsA), the authors explored whether RA susceptibility genes are also associated with PsA.

**Methods** 56 single nucleotide polymorphisms (SNPs) mapping to 41 genes previously reported as RA susceptibility loci were selected for investigation. PsA was defined as an inflammatory arthritis associated with psoriasis and subjects were recruited from the UK and Ireland. Genotyping was performed using the Sequenom MassArray platform and frequencies compared with data derived from large UK control collections.

**Results** Significant evidence for association with susceptibility to PsA was found to a SNP mapping to the *REL* (rs13017599,  $p_{\text{trend}}=5.2\times 10^{-4}$ ) gene, while nominal evidence for association ( $p_{\text{trend}}<0.05$ ) was found to seven other loci including *PLCL2* (rs4535211,  $p=1.7\times 10^{-3}$ ); *STAT4* (rs10181656,  $p=3.0\times 10^{-3}$ ) and the *AFF3*, *CD28*, *CCL21*, *IL2* and *KIF5A* loci. Interestingly, three SNPs demonstrated opposite effects to those reported for RA.

**Conclusions** The *REL* gene, a key modulator of the NF $\kappa$ B pathway, is associated with PsA but the allele conferring risk to RA is protective in PsA suggesting that there are fundamental differences in the aetiological mechanisms underlying these two types of inflammatory arthritis.

## INTRODUCTION

Psoriatic arthritis (PsA) shares many features in common with rheumatoid arthritis (RA). For example, both diseases are characterised by the occurrence of an inflammatory arthritis in peripheral synovial joints; both respond to similar therapies including Methotrexate and anti-tumour necrosis factor biologic treatment and both are complex diseases with genetic and environmental components to susceptibility. Much progress has been made in identifying RA susceptibility genes as a result of genome-wide association studies with a recent meta-analysis listing 31 loci with confirmed evidence for association.<sup>1</sup> What is remarkable is the degree of overlap of RA loci with loci identified in other autoimmune diseases including type 1 diabetes, systemic lupus erythematosus and coeliac disease, for example.<sup>2</sup>

Those autoimmune diseases are characterised by the presence of autoantibodies and differ from PsA in that respect. However, given the overlap of clinical features between RA and PsA, it might be expected that there would be some overlap in the genetic susceptibility.

The two major RA susceptibility genes are the *HLA DRB1* and *PTPN22* genes but previous investigations have largely reported no evidence for association with PsA.<sup>4–8</sup> Few of the other loci have been investigated, to date. The aim of the current study was to investigate association of 41 suggestive and confirmed RA susceptibility loci with PsA in a large UK cohort.

## METHODS

### Patient samples

A total of 1057 Genomic DNA samples collected from PsA patients of White European ancestry were available via the collaboration of three UK rheumatology centres and one centre in Ireland (885 UK and 172 Ireland), details of which have been described previously.<sup>9–11</sup> PsA classification was defined as 'an inflammatory arthritis associated with psoriasis, which is usually negative for rheumatoid factor'.<sup>12</sup> This study was approved by the North West Multicentre Research Ethics Committee (MREC 99/8/84). All subjects provided informed consent.

### Control samples

Single nucleotide polymorphism (SNP) genotype data were available for healthy controls from the 1958 British Birth Cohort and the UK Blood Service Collection. Both cohorts were genotyped on the Illumina Human1M-Duo and Affymetrix Genome-wide Human SNP Array 6.0 as part of the Wellcome Trust Case-Control Consortium 2 (WTCCC2) project ([www.wtccc.org.uk](http://www.wtccc.org.uk)). A total of 4000 genomic DNA samples were available for in-house genotyping of SNPs not represented on these arrays.

### SNP selection

RA susceptibility SNPs were selected for genotyping if they were considered as confirmed associations or demonstrated suggestive evidence for association from a number of well-powered published reports.<sup>1–23</sup>



## Genotyping

SNP genotyping of the PsA, 1958 birth cohort and Ireland control samples was performed using Sequenom's MassARRAY system (San Diego, California, USA) according to the manufacturers' specifications for the iPLEX chemistry using 10 ng of genomic DNA. Cluster plots for all SNPs were manually evaluated to confirm satisfactory performance. SNPs observed to have poor clustering characteristics were excluded from further analysis.

## Statistical analysis

All quality control steps and statistical analyses were performed using the PLINK software package.<sup>24</sup> Missing data rates for inclusion of both SNPs and samples were set at <10%. Test statistics for Hardy–Weinberg equilibrium using an exact test, the Cochran–Armitage trend test and OR (including 95% CI) were calculated for the combined UK and Ireland dataset. To explicitly control for any bias introduced by population stratification, we analysed each population separately and combined the results via inverse-variance meta-analysis under the assumption of fixed effects. Allelic heterogeneity between the two groups was estimated using the Cochran Q and  $I^2$  statistics. A p value of <0.0015 was regarded as statistically significant after applying a Bonferroni correction for the number of loci tested. Nominal associations were those at p <0.05.

Subphenotype analysis was performed within the PsA dataset based on, first, the age at onset of psoriasis (type I psoriasis has an onset ≤40 years of age while type II psoriasis is defined as an onset >40 years of age, n=354 and 540, respectively) and, second, seronegativity for rheumatoid factor (n=179) in an attempt to exclude those patients who may have PsV and coexisting RA. All subphenotype analyses were performed in UK samples only.

## RESULTS

### SNP selection

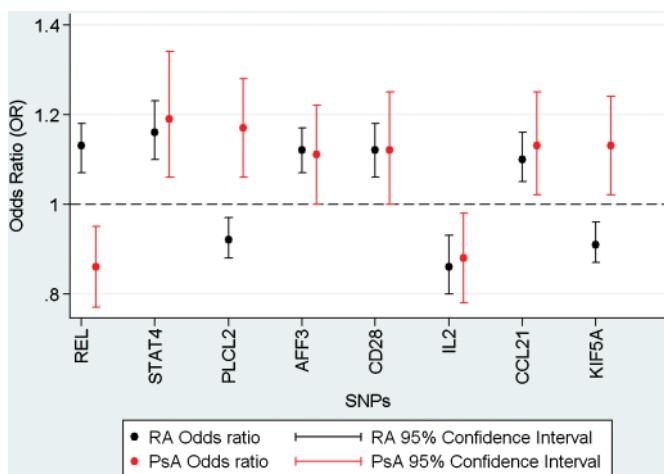
A total of 56 SNPs mapping to 41 genomic regions previously reported as suggestive or confirmed susceptibility loci for RA were selected from published reports (see online supplementary table S1).

## Genotyping

Eight of the selected SNPs failed inclusion during assay design and a further five SNPs were excluded due to unsatisfactory genotype clustering. Following the removal of samples and SNPs with high levels of missing data there were a maximum of 982 PsA cases, 2925 controls from the 1958 birth cohort (genotyped in-house), 371 Ireland controls and 5380 controls from the WTCCC2 data (see online supplementary table S2).

## Statistical analysis

Investigation of the 43 successfully genotyped SNPs identified significant association ( $p_{\text{trend}} < 0.0015$ ) with one SNP, rs13017599 (*REL*), in the dataset as a whole (table 1) and when analysis was restricted to the UK dataset ( $p_{\text{trend}} = 0.001$ , online supplementary table S2). The rs453211 (*PLCL2*) and rs10181656 (*STAT4*) SNPs were associated at nominal thresholds in the entire dataset (0.0016 and 0.003, respectively, table 1) and UK-only subgroups ( $p_{\text{trend}} = 0.009$ ,  $p_{\text{trend}} = 0.02$  respectively, online supplementary table S2). In addition, the analysis reveals nominal association ( $p_{\text{trend}} < 0.05$ ) to six SNPs: rs10865035 (*AFF3*), rs1980422 (*CD28*), rs2069778 (*IL2*), rs13192841 (*TNFAIP3*), rs2812378 (*CCL21*) and rs3184504 (*KIF5A*) in the combined UK and Ireland dataset but not when restricted to UK samples alone (table 1, online supplementary table S2). Interestingly, at three of the associated loci



**Figure 1** OR plots for eight SNPs demonstrating evidence for association to PsA susceptibility, highlighting the opposing direction of effects for *REL*, *PLCL2* and *KIF5A*. PsA, psoriatic arthritis; RA, rheumatoid arthritis, SNP, single nucleotide polymorphism.

(*REL*, *PLCL2* and *STAT4*) the direction of the effect was opposite to that reported in the RA studies (figure 1).

Subphenotype analysis revealed a greater effect for the *REL* SNP, rs13017599, in the late onset psoriasis (type II) and the sero-negative subgroups of PsA (see online supplementary table S3). Conversely, the association to the *PLCL2* SNP, rs453211, was wholly restricted to the early onset psoriasis subgroup (type I) (see online supplementary table S3). While these associations are intriguing, their interpretation should be tempered by acknowledging the limited number of samples in these subgroups.

## DISCUSSION

We have undertaken a comprehensive analysis testing established RA susceptibility loci for association with PsA. We have found significant evidence for association with the *REL* locus and nominal evidence for association with seven other RA susceptibility SNPs. Interestingly, for three of the eight PsA-associated variants, the risk allele is opposite to that reported in RA.

Given the phenotypic similarities between RA and PsA, it was expected that some genetic overlap would be observed as the concept is well established for autoimmune diseases such as RA, systemic lupus erythematosus and type 1 diabetes.<sup>25</sup> However, it could also be argued that inflammatory arthritis may be an outcome of different immune responses in joints caused by different triggers with different underlying genetic susceptibility. Indeed, enthesitis is thought to be the primary abnormality in PsA by many researchers, with synovitis being a secondary phenomenon, in contrast to RA where the synovitis takes primacy. The results of this genetic study support a mixed picture of genetic overlap between RA and PsA, with some RA loci showing association with the same allele, some with the opposite allele and some showing no association with PsA.

Association of different autoimmune diseases with opposite alleles of the same susceptibility variant has been reported previously. For example, the minor T allele of the *PTPN22* rs2476601 SNP confers susceptibility to RA, type 1 diabetes and autoimmune thyroid disease while the major C allele confers susceptibility to Crohn's disease.<sup>25</sup> Similarly, association at the *REL* locus SNP, rs13017599, has been reported previously in psoriasis but the opposite allele has also been associated with RA.<sup>26,27</sup> These findings may suggest that RA clusters with the classical autoantibody associated autoimmune diseases, while PsA shares greater genetic similarity

to psoriasis and seronegative diseases, such as Crohn's disease. It is possible that these SNPs may be markers for susceptibility to psoriasis and not specific to PsA. It would be of great interest to test these markers in a cohort of psoriasis patients screened to exclude samples with evidence of inflammatory arthritis.

The conclusions that can be drawn are necessarily limited by the limitations of the study design. Many of the RA susceptibility loci examined have modest effect sizes that the current study was underpowered to reliably detect online supplementary table S1. It may be that more RA susceptibility loci are associated with PsA than detected currently, therefore. For example, the study had only limited power to detect association at a number of the loci. This power is further reduced by using a Bonferroni corrected p value threshold and so there may be a number of false negative results. For this reason, we have reported loci showing nominal as well as significant evidence for association although replication is required for all these SNPs in additional datasets before they can be confidently labelled as PsA susceptibility loci. Ultimately, a full understanding of the extent of overlap between PsA and RA susceptibility loci will require comparison of well-powered genome-wide association studies in the two diseases.

A further limitation of the study design is the testing of only one or a small number of variants at each locus. It may be that different variants at the locus are more strongly associated with PsA; for example, different variants at the *TNFAIP3* gene are associated with systemic lupus erythematosus, RA and psoriasis.<sup>18–21</sup> Investigation of this possibility will require analysis of detailed fine mapping data of RA associated genomic loci in PsA samples.

The strongest evidence for association was with the *REL* locus where two SNPs showed association but only one remained significant at the corrected threshold (rs13017599). The *REL* locus, which encodes c-REL, a member of the NF $\kappa$ B inflammatory pathway, has been reported to be associated with type I psoriasis in a large genome-wide association study but with a different SNP, rs702873 (OR 1.12).<sup>27</sup> There is strong, but not complete, correlation ( $r^2=0.76$  with rs13017599) between the two variants suggesting that the primary association is with psoriasis rather than PsA. The robust identification of PsA specific variants would require a collection of patients with uncomplicated psoriasis, where patients have been screened for the absence of inflammatory arthritis. Unfortunately, such a collection is not currently available to our research group.

Interestingly, the subphenotype analysis in the PsA samples suggests that the association may be even stronger in type II psoriasis compared with the cohort as a whole (OR 1.47 vs 1.19, based on allele G as the risk allele) but this requires confirmation in other cohorts.

Association with *PLCL2* has not been reported previously with psoriasis and it shows only borderline evidence for association in the current study when using the Bonferroni corrected p value. Furthermore, association of this locus with RA remains suggestive rather than confirmed at genome-wide significance thresholds and hence this result may represent a false positive finding. Nonetheless, it is of interest because the gene encodes a negative regulator of B cell receptor signalling, important in controlling immune responses and, again, the allele conferring risk to RA is protective for PsA.<sup>15</sup>

Of the other loci with nominal evidence for association, *STAT4* has been reported to be associated with psoriasis previously in a Greek population.<sup>32</sup> The reported SNP, rs7574865, is highly correlated with rs10181656 reported in this study ( $r^2=1.00$ ). Interestingly, the allele associated with RA susceptibility

conferred protection to PsA. Association at the *IL2/21* locus has been reported previously with a different SNP (rs13151961  $r^2=1.00$ ) in a US PsA cohort<sup>33</sup> and with the same SNP in a UK psoriasis cohort.<sup>34</sup>

An important point is that the majority of RA risk loci are identified using patients positive for anticyclic citrullinated peptide antibodies. Given the importance of seronegativity in the classification of PsA, it would be interesting to evaluate susceptibility risk loci identified in anticyclic citrullinated peptide antibody negative RA samples. However, to date there are no robustly confirmed susceptibility loci for seronegative RA.

In summary, we report significant evidence for association of the *REL* locus with PsA and nominal evidence for association with eight other RA associated SNPs. For a significant minority of the loci, opposing alleles confer risk to PsA and RA suggesting that there are fundamental differences in the aetiological mechanisms underlying these two types of inflammatory arthritis.

**Contributors** AB was responsible for concept and design, initiated the collaborative effort, contributed to interpretation of results, and drafted and revised the final manuscript. She is the guarantor. JB performed data quality control, statistical analysis and interpretation of results, and drafted and revised the final manuscript. He is the guarantor. EF performed laboratory data collection and data quality control. FA was involved in statistical analysis. PH, HM-O, LC, RBW, RM, AWR, DK, EK, NM, OF, JP, AWM and INB were involved in the collaborative effort to collect biological samples. In addition, all authors were also responsible for critically reviewing the draft manuscript and approving the final version.

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Marker	chr	gene	Reported association				Study power	Reference
			Minor allele	MAF	Odds Ratio (95% CI)	p-value		
rs3890745	1p36	TNFRSF14	C	0.32	0.89 (0.85-0.94)	3,60E-06	0.41	Stahl <i>et al</i> 2010
rs2476601	1p13	PTPN22	A	0.10	1.94 (1.81-2.08)	9,10E-74	0.99	Stahl <i>et al</i> 2010
rs11586238	1p13	CD2	G	0.24	1.13 (1.07-1.19)	1,00E-05	0.44	Stahl <i>et al</i> 2010
rs7543174	1q21	IL6R	C	0.18	1.07 (1.01-1.13)	1,20E-05	0.16	Stahl <i>et al</i> 2010
rs12746613	1q23	FCGR2A	T	0.12	1.13 (1.06-1.21)	4,00E-04	0.34	Stahl <i>et al</i> 2010
rs840016	1q24	CD247	T	0.42	0.92 (0.86-0.98)	1,60E-06	0.22	Stahl <i>et al</i> 2010
rs10919563	1q31	PTPRC	A	0.13	0.88 (0.82-0.94)	2,00E-04	0.36	Stahl <i>et al</i> 2010
rs13031237	2p16	REL	T	0.37	1.13 (1.07-1.18)	7,90E-07	0.43	Stahl <i>et al</i> 2010
rs13017599	2p16	REL	A	0.34	1.21 (1.15-1.28)	2,60E-12	0.80	Gregersen <i>et al</i> 2009
rs1160542	2q11	AFF3	G	0.46	1.11 (1.07-1.16)	1,15E-07	0.29	Plant <i>et al</i> 2010
rs10865035	2q11	AFF3	A	0.47	1.12 (1.07-1.17)	2,00E-06	0.32	Stahl <i>et al</i> 2010
rs11676922	2q11	AFF3	T	0.46	1.15 (1.10-1.20)	1,00E-14	0.46	Stahl <i>et al</i> 2010
rs934734	2q14	SPRED2	G	0.49	1.13 (1.06-1.21)	5,30E-10	0.35	Stahl <i>et al</i> 2010
rs10181656	2q32	STAT4	G	0.22	1.14 (1.07-1.21)	4,00E-05	0.49	Barton <i>et al</i> 2008
rs1980422	2q33	CD28	C	0.24	1.12 (1.06-1.18)	5,20E-05	0.39	Stahl <i>et al</i> 2010
rs231775	2q33	CTLA4	A	0.49	0.86 (0.81-0.90)	6,25E-09	0.52	Gregersen <i>et al</i> 2009
rs3087243	2q33	CTLA4	A	0.44	0.87 (0.83-0.91)	1,20E-08	0.50	Stahl <i>et al</i> 2010
rs4535211*	3p24	PLCL2	A	0.46	0.96	8,90E-05	0.09	Raychaudhuri <i>et al</i> 2009
rs13315591	3p14	PXX	C	0.08	1.13 (1.04-1.23)	4,60E-08	0.27	Stahl <i>et al</i> 2010
rs874040	4p15	RBPJ	C	0.30	1.18 (1.12-1.24)	1,00E-16	0.69	Stahl <i>et al</i> 2010
rs2069778	4q27	IL2	G	0.18	0.78 (0.68-0.89)	3,00E-04	0.92	Coenen <i>et al</i> 2009
rs6822844	4q27	IL21	T	0.18	0.88 (0.84-0.92)	5,89E-08	0.42	Plant <i>et al</i> 2010
rs13119723	4q27	IL21	G	0.15	0.87 (0.81-0.93)	6,80E-07	0.45	Stahl <i>et al</i> 2010
rs6859219	5q11	ANKRD55	A	0.21	0.85 (0.78-0.93)	6,90E-10	0.64	Stahl <i>et al</i> 2010
rs10040327†	5q11	ANKRD55	-	-	-	2,70E-11	-	Stahl <i>et al</i> 2010
rs26232	5q21	C5orf30	T	0.32	0.93 (0.88-0.98)	4,10E-08	0.19	Stahl <i>et al</i> 2010
rs548234	6q21	PRDM1	C	0.33	1.10 (1.05-1.16)	9,70E-05	0.29	Stahl <i>et al</i> 2010
rs13207033‡	6q23	TNFAIP3	A	0.27	0.90 (0.86-0.94)	2,52E-07	0.35	Plant <i>et al</i> 2010
rs6920220	6q23	TNFAIP3	A	0.22	1.22 (1.16-1.29)	8,90E-13	0.83	Stahl <i>et al</i> 2010
rs5029937	6q23	TNFAIP3	T	0.04	1.40 (1.24-1.58)	7,50E-08	0.84	Stahl <i>et al</i> 2010
rs394581	6q25	TAGAP	C	0.30	0.91 (0.87-0.96)	6,00E-04	0.29	Stahl <i>et al</i> 2010
rs3093023	6q27	CCR6	A	0.43	1.11 (1.06-1.16)	4,20E-11	0.30	Stahl <i>et al</i> 2010
rs42041*	7q21	CDK6	G	0.26	1.08	4,00E-06	0.21	Raychaudhuri <i>et al</i> 2008
rs10488631	7q32	IRF5	C	0.10	1.25 (1.14-1.37)	4,20E-11	0.78	Stahl <i>et al</i> 2010
rs2736340	8p23	BLK	A	0.24	1.19 (1.13-1.27)	5,69E-09	0.73	Gregersen <i>et al</i> 2009
rs2812378	9p13	CCL21	G	0.34	1.10 (1.05-1.16)	1,00E-04	0.29	Raychaudhuri <i>et al</i> 2009
rs951005	9p13	CCL21	G	0.15	0.87 (0.81-0.93)	3,90E-10	0.45	Stahl <i>et al</i> 2010
rs10760130‡	9q33	TRAF1/C5	G	0.43	1.13 (1.08-1.18)	2,10E-07	0.39	Stahl <i>et al</i> 2010
rs2900180	9q33	TRAF1/C5	T	0.30	1.34 (1.24-1.45)	8,00E-14	0.99	Plenge <i>et al</i> 2007
rs706778	10p15	IL2RA	T	0.40	1.11 (1.06-1.17)	1,40E-11	0.32	Stahl <i>et al</i> 2010
rs2104286	10p15	IL2RA	C	0.27	0.92 (0.87-0.97)	2,00E-03	0.24	Stahl <i>et al</i> 2010
rs11594656	10p15	IL2RA	A	0.25	0.95 (0.90-1.00)	1,00E-04	0.12	Stahl <i>et al</i> 2010
rs4750316	10p15	PRKCQ	C	0.19	0.87 (0.82-0.92)	2,00E-06	0.50	Stahl <i>et al</i> 2010
rs2793108	10p11	ZEB1	C	0.43	0.93 (0.89-0.98)	1,40E-05	0.38	Stahl <i>et al</i> 2010
rs540386	11p12	TRAF6	T	0.14	0.88 (0.83-0.94)	3,00E-04	0.38	Stahl <i>et al</i> 2010
rs1678542	12q13	KIF5A	G	0.38	0.91 (0.87-0.96)	2,00E-04	0.28	Stahl <i>et al</i> 2010
rs3184504	12q24	SH2B3	C	0.49	0.92 (0.88-0.96)	6,00E-06	0.20	Stahl <i>et al</i> 2010
rs7155603	14q24	BATF	G	0.19	1.12 (1.04-1.20)	1,10E-07	0.37	Stahl <i>et al</i> 2010
rs8045689	16p11	CD19	C	0.30	1.06 (1.01-1.12)	2,40E-05	0.14	Stahl <i>et al</i> 2010
rs2872507	17q12	IKZF3	A	0.47	1.08 (1.02-1.14)	9,40E-07	0.18	Stahl <i>et al</i> 2010
rs7234029	18p11	PTNP2	G	0.16	1.13 (1.06-1.20)	1,00E-04	0.39	Stahl <i>et al</i> 2010
rs4810485	20q13	CD40	T	0.25	0.85 (0.80-0.90)	2,80E-09	0.67	Stahl <i>et al</i> 2010
rs11203203	21q22	UBASH3A	A	0.37	1.07 (1.00-1.14)	3,80E-06	0.17	Stahl <i>et al</i> 2010
rs5754217	22q11	UBE2L3	T	0.19	1.07 (1.01-1.13)	4,80E-05	0.16	Stahl <i>et al</i> 2010
rs3218258	22q12	IL2RB	A	0.26	1.13 (1.07-1.18)	1,30E-06	0.45	Barton <i>et al</i> 2008
rs743777	22q12	IL2RB	G	0.31	1.11 (1.05-1.17)	4,60E-08	0.34	Barton <i>et al</i> 2008

Summary of reported association statistics for the 57 selected rheumatoid arthritis susceptibility SNPs and statistical power of the current to detect an effect of similar magnitude. (chr = chromosome, MAF = minor allele frequency, CI = confidence intervals).

\*no confidence intervals reported, † insufficient information.









rs	chr	pos	gene	allele1	allele2	subphenotype	Frq_aff	Frq_unaff	case_n	gen_cnt_aff	gen_frq_aff	cont_n	gen_cnt_unaff	gen_frq_unaff	hwe_unaff	hwe_aff	trend	OR	ci_l_95	ci_u_95
rs540386	11	36481869	TRAF6	T	C	seronegative	0,1433	0,132	349	9/82/258	2.6/23.5/73.9	5374	90/1239/4045	1.7/23.1/75.3	0,7209	0,3869	0,3956	1,099	0,8832	1,369
rs540386	11	36481869	TRAF6	T	C	Type I	0,1368	0,132	519	9/124/386	1.7/23.9/74.4	5374	90/1239/4045	1.7/23.1/75.3	0,7209	1	0,6636	1,042	0,8654	1,254
rs540386	11	36481869	TRAF6	T	C	Type II	0,1243	0,132	173	6/31/136	3.5/17.9/78.6	5374	90/1239/4045	1.7/23.1/75.3	0,7209	0,02879	0,6749	0,933	0,6746	1,29
rs1678542	12	56254982	KIF5A	G	C	seronegative	0,3742	0,3757	322	44/153/125	13.7/47.5/38.8	5352	771/2480/2101	14.4/46.3/39.3	0,3666	0,9052	0,9385	0,9935	0,843	1,171
rs1678542	12	56254982	KIF5A	G	C	Type I	0,376	0,3757	508	68/246/194	13.4/48.4/38.2	5352	771/2480/2101	14.4/46.3/39.3	0,3666	0,5087	0,9882	1,001	0,8765	1,143
rs1678542	12	56254982	KIF5A	G	C	Type II	0,3669	0,3757	169	25/74/70	14.8/43.8/41.4	5352	771/2480/2101	14.4/46.3/39.3	0,3666	0,5073	0,7415	0,9627	0,769	1,205
rs3184504	12	110368991	SH2B3	T	C	seronegative	0,5115	0,4886	347	91/173/83	26.2/49.9/23.9	5193	1217/2641/1335	23.4/50.9/25.7	0,2115	1	0,239	1,096	0,9397	1,278
rs3184504	12	110368991	SH2B3	T	C	Type I	0,5283	0,4886	513	143/256/114	27.9/49.9/22.2	5193	1217/2641/1335	23.4/50.9/25.7	0,2115	1	0,01464	1,172	1,031	1,333
rs3184504	12	110368991	SH2B3	T	C	Type II	0,4588	0,4886	170	36/84/50	21.2/49.4/29.4	5193	1217/2641/1335	23.4/50.9/25.7	0,2115	1	0,275	0,8873	0,7144	1,102
rs7234029	18	12867060	PTNP2	G	A	seronegative	0,1719	0,1553	349	12/96/241	3.4/27.5/69.1	5369	118/1432/3819	2.2/26.7/71.1	0,2524	0,5713	0,2393	1,129	0,9211	1,384
rs7234029	18	12867060	PTNP2	G	A	Type I	0,1686	0,1553	519	14/147/358	2.7/28.3/69.0	5369	118/1432/3819	2.2/26.7/71.1	0,2524	1	0,2578	1,103	0,9296	1,308
rs7234029	18	12867060	PTNP2	G	A	Type II	0,1618	0,1553	173	6/44/123	3.5/25.4/71.1	5369	118/1432/3819	2.2/26.7/71.1	0,2524	0,4011	0,7404	1,05	0,7851	1,404
rs4810485	20	44181354	CD40	T	G	seronegative	0,2461	0,2386	323	20/119/184	6.2/36.8/57.0	5352	313/1928/3111	5.8/36.0/58.1	0,5227	0,8813	0,6644	1,042	0,8664	1,253
rs4810485	20	44181354	CD40	T	G	Type I	0,2407	0,2386	509	32/181/296	6.3/35.6/58.2	5352	313/1928/3111	5.8/36.0/58.1	0,5227	0,5447	0,8832	1,011	0,8702	1,176
rs4810485	20	44181354	CD40	T	G	Type II	0,2441	0,2386	170	11/61/98	6.5/35.9/57.6	5352	313/1928/3111	5.8/36.0/58.1	0,5227	0,6812	0,8152	1,031	0,8015	1,325
rs11203203	21	42709255	UBASH3A	A	G	seronegative	0,342	0,3741	345	41/154/150	11.9/44.6/43.5	5377	739/2545/2093	13.7/47.3/38.9	0,449	0,9048	0,08969	0,8697	0,7396	1,023
rs11203203	21	42709255	UBASH3A	A	G	Type I	0,3706	0,3741	514	71/239/204	13.8/46.5/39.7	5377	739/2545/2093	13.7/47.3/38.9	0,449	0,9249	0,8252	0,9853	0,863	1,125
rs11203203	21	42709255	UBASH3A	A	G	Type II	0,3081	0,3741	172	14/78/80	8.1/45.3/46.5	5377	739/2545/2093	13.7/47.3/38.9	0,449	0,4767	0,01221	0,7452	0,5908	0,9399
rs3218258	22	35874191	IL2RB	A	G	seronegative	0,2712	0,2626	354	21/150/183	5.9/42.4/51.7	5198	353/2024/2821	6.8/38.9/54.3	0,7203	0,2255	0,614	1,045	0,8803	1,24
rs3218258	22	35874191	IL2RB	A	G	Type I	0,2774	0,2626	539	44/211/284	8.2/39.1/52.7	5198	353/2024/2821	6.8/38.9/54.3	0,7203	0,5915	0,2946	1,078	0,9367	1,24
rs3218258	22	35874191	IL2RB	A	G	Type II	0,2697	0,2626	178	10/76/92	5.6/42.7/51.7	5198	353/2024/2821	6.8/38.9/54.3	0,7203	0,3416	0,765	1,037	0,8171	1,316
rs743777	22	35881553	IL2RB	G	A	seronegative	0,3297	0,3107	323	30/153/140	9.3/47.4/43.3	5352	512/2302/2538	9.6/43.0/47.4	0,774	0,2566	0,3095	1,091	0,9215	1,292
rs743777	22	35881553	IL2RB	G	A	Type I	0,3173	0,3107	509	50/223/236	9.8/43.8/46.4	5352	512/2302/2538	9.6/43.0/47.4	0,774	0,8384	0,6648	1,031	0,8979	1,184
rs743777	22	35881553	IL2RB	G	A	Type II	0,3412	0,3107	170	16/84/70	9.4/49.4/41.2	5352	512/2302/2538	9.6/43.0/47.4	0,774	0,2345	0,231	1,149	0,9146	1,443