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, $p_{trend}=5.2\times10^{4}$) gene, while nominal evidence for association ($p_{trend}<0.05$) was found to seven other loci including *PLCL2* (rs4535211, $p=1.7\times10^{-3}$); *STAT4* (rs10181656, $p=3.0\times10^{-3}$) 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 NFκB 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.[1] 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.[2 3] 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.[4–8] 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.[9–11] PsA classification was defined as 'an inflammatory arthritis associated with psoriasis, which is usually negative for rheumatoid factor'.[12] 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). 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.[1 13–23]

Table 1 Association statistics for susceptibility to psoriatic arthritis for the 44 successfully genotype SNPs

			Number		MAF		Genotype counts		Genotype frequencies		HWE		p Value		95% CI	
Marker	Chr	Gene	Case	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Trend	OR	Lower	Upper
rs2476601	1	*PTPN22*	982	5568	0.11	0.10	15/185/782	45/991/4532	1.5/18.8/79.6	0.8/17.8/81.4	0.323	0.284	0.08863	1.14	0.98	1.34
rs11586238	1	*CD2*	980	5750	0.24	0.23	65/342/573	330/2036/3384	6.6/34.9/58.5	5.7/35.4/58.9	0.162	0.304	0.5419	1.04	0.93	1.16
rs7543174	1	*IL6R*	972	5560	0.17	0.18	25/277/670	174/1656/3730	2.6/28.5/68.9	3.1/29.8/67.1	0.647	0.586	0.2	0.92	0.81	1.05
rs13031237	2	*REL*	972	5560	0.34	0.38	115/431/426	781/2617/2162	11.8/44.3/43.8	14.0/47.1/38.9	0.721	0.819	0.002569	0.86	0.77	0.95
rs13017599	2	*REL*	971	5553	0.33	0.38	107/436/428	781/2612/2160	11.0/44.9/44.1	14.1/47.0/38.9	0.829	0.864	0.0005242	0.84	0.75	0.93
rs1160542	2	*AFF3*	981	5568	0.47	0.46	229/472/280	1157/2798/1613	23.3/48.1/28.5	20.8/50.3/29.0	0.277	0.388	0.2194	1.06	0.96	1.17
rs10865035	2	*AFF3*	981	3296	0.48	0.46	237/472/272	667/1678/951	24.2/48.1/27.7	20.2/50.9/28.9	0.250	0.150	0.04775	1.11	1.00	1.22
rs10181656	2	*STAT4*	980	3832	0.25	0.22	67/359/554	180/1327/2325	6.8/36.6/56.5	4.7/34.6/60.7	0.397	0.638	0.003032	1.19	1.06	1.34
rs1980422	2	*CD28*	975	5747	0.25	0.23	54/372/549	273/2051/3423	5.5/38.2/56.3	4.8/35.7/59.6	0.437	0.131	0.0471	1.12	1.00	1.25
rs231775	2	*CTLA4*	971	5568	0.39	0.39	144/468/359	852/2675/2041	14.8/48.2/37.0	15.3/48.0/36.7	0.686	0.633	0.7419	0.98	0.89	1.09
rs3087243	2	*CTLA4*	978	5748	0.43	0.44	162/511/305	1126/2850/1772	16.6/52.2/31.2	19.6/49.6/30.8	0.037	0.749	0.1609	0.93	0.85	1.03
rs4535211	3	*PLCL2*	975	5745	0.53	0.49	262/503/210	1376/2857/1512	26.9/51.6/21.5	24.0/49.7/26.3	0.304	0.712	0.001663	1.17	1.06	1.28
rs13315591	3	*FAM107A*	973	5740	0.09	0.08	6/164/803	37/878/4825	0.6/16.9/82.5	0.6/15.3/84.1	0.560	0.729	0.2671	1.10	0.93	1.30
rs874040	4	*RBPJ*	972	5704	0.32	0.30	100/423/449	511/2404/2789	10.3/43.5/46.2	9.0/42.1/48.9	1.000	0.850	0.0736	1.10	0.99	1.22
rs2069778	4	*IL2*	960	3699	0.16	0.18	19/269/672	124/1086/2489	2.0/28.0/70.0	3.4/29.4/67.3	0.229	0.697	0.03611	0.87	0.76	0.99
rs6822844	4	*IL21*	958	5549	0.16	0.17	20/264/674	155/1631/3763	2.1/27.6/70.4	2.8/29.4/67.8	0.396	0.178	0.07937	0.89	0.78	1.02
rs10040327	5	*ANKRD55*	970	5737	0.10	0.12	7/186/777	102/1139/4496	0.7/19.2/80.1	1.8/19.9/78.4	0.300	0.004	0.07912	0.87	0.74	1.01
rs26232	5	*C5orf30*	972	5558	0.32	0.33	95/430/447	575/2511/2472	9.8/44.2/46.0	10.3/45.2/44.5	0.606	0.095	0.3614	0.95	0.86	1.06
rs548234	6	*PRDM1*	980	5751	0.31	0.33	92/423/465	604/2599/2548	9.4/43.2/47.4	10.5/45.2/44.3	0.823	0.129	0.06098	0.91	0.82	1.01
rs13207033	6	*TNFAIP3*	960	5723	0.26	0.28	63/371/526	451/2260/3012	6.6/38.6/54.8	7.9/39.5/52.6	0.867	0.355	0.1154	0.92	0.82	1.02
rs6920220	6	*TNFAIP3*	959	5723	0.21	0.22	48/312/599	289/1968/3466	5.0/32.5/62.5	5.0/34.4/60.6	0.385	0.647	0.3449	0.94	0.84	1.06
rs5029937	6	*TNFAIP3*	956	3447	0.03	0.03	2/52/902	5/229/3213	0.2/5.4/94.4	0.1/6.6/93.2	0.191	0.607	0.2508	0.84	0.63	1.13
rs394581	6	*TAGAP*	978	2988	0.32	0.31	102/417/459	298/1271/1419	10.4/42.6/46.9	10.0/42.5/47.5	0.606	0.580	0.6767	1.02	0.92	1.14
rs3093023	6	*CCR6*	968	5735	0.42	0.43	146/523/299	1099/2778/1858	15.1/54.0/30.9	19.2/48.4/32.4	0.001	0.295	0.29	0.95	0.86	1.05
rs42041	7	*CDK6*	982	5747	0.26	0.25	62/387/533	342/2144/3261	6.3/39.4/54.3	6.0/37.3/56.7	0.507	0.696	0.1781	1.08	0.97	1.20
rs10488631	7	*IRF5*	973	5559	0.11	0.11	14/194/765	59/1085/4415	1.4/19.9/78.6	1.1/19.5/79.4	0.635	0.444	0.4412	1.06	0.91	1.24
rs2736340	8	*BLK*	971	5741	0.24	0.25	50/373/548	330/2158/3253	5.1/38.4/56.4	5.7/37.6/56.7	0.222	0.269	0.8585	0.99	0.89	1.11
rs2812378	9	*CCL21*	960	5723	0.37	0.34	138/433/389	643/2615/2465	14.4/45.1/40.5	11.2/45.7/43.1	0.332	0.206	0.01475	1.13	1.02	1.25
rs951005	9	*CCL21*	973	5558	0.16	0.15	27/249/697	111/1406/4041	2.8/25.6/71.6	2.0/25.3/72.7	0.394	0.421	0.2876	1.08	0.94	1.23
rs10760130	9	*TRAF1/C5*	959	5549	0.44	0.44	189/466/304	1089/2680/1780	19.7/48.6/31.7	19.6/48.3/32.1	0.694	0.164	0.8523	1.01	0.92	1.11
rs2900180	9	*TRAF1/C5*	982	5570	0.35	0.35	120/445/417	706/2479/2385	12.2/45.3/42.5	12.7/44.5/42.8	0.944	0.118	0.9659	1.00	0.90	1.10
rs706778	10	*IL2RA*	965	5740	0.42	0.40	193/432/340	936/2737/2067	20.0/44.8/35.2	16.3/47.7/36.0	0.010	0.564	0.06669	1.10	0.99	1.21
rs2104286	10	*IL2RA*	980	5743	0.27	0.28	73/390/517	462/2297/2984	7.4/39.8/52.8	8.0/40.0/52.0	1.000	0.493	0.5272	0.97	0.87	1.08
rs11594656	10	*IL2RA*	976	5749	0.23	0.24	66/320/590	342/2087/3320	6.8/32.8/60.5	5.9/36.3/57.7	0.015	0.564	0.3705	0.95	0.85	1.06
rs4750316	10	*PRKCQ*	982	5749	0.17	0.19	24/290/668	222/1745/3782	2.4/29.5/68.0	3.9/30.4/65.8	0.313	0.248	0.0562	0.88	0.78	1.00
rs540386	11	*TRAF6*	973	5736	0.14	0.13	24/215/734	101/1327/4308	2.5/22.1/75.4	1.8/23.1/75.1	0.098	0.955	0.8234	1.02	0.88	1.17
rs1678542	12	*KIF5A*	958	5723	0.42	0.39	184/434/340	896/2675/2152	19.2/45.3/35.5	15.7/46.7/37.6	0.034	0.182	0.02048	1.13	1.02	1.24
rs3184504	12	*SH2B3*	963	5555	0.50	0.49	248/467/248	1298/2819/1438	25.8/48.5/25.8	23.4/50.7/25.9	0.367	0.248	0.305	1.05	0.95	1.16
rs7234029	18	*PTNP2*	972	5731	0.17	0.16	24/273/675	128/1536/4067	2.5/28.1/69.4	2.2/26.8/71.0	0.642	0.249	0.3219	1.07	0.94	1.22
rs4810485	20	*CD40*	960	5723	0.25	0.24	66/354/540	332/2088/3303	6.9/36.9/56.2	5.8/36.5/57.7	0.443	0.942	0.2308	1.07	0.96	1.20
rs11203203	21	*UBASH3A*	966	5731	0.35	0.37	119/440/407	786/2696/2249	12.3/45.5/42.1	13.7/47.0/39.2	1.000	0.651	0.07026	0.91	0.82	1.01
rs3218258	22	*IL2RB*	979	5569	0.27	0.26	76/379/524	381/2161/3027	7.8/38.7/53.5	6.8/38.8/54.4	0.518	0.890	0.4175	1.05	0.94	1.17
rs743777	22	*IL2RB*	960	5723	0.33	0.31	100/431/429	549/2450/2724	10.4/44.9/44.7	9.6/42.8/47.6	0.609	0.975	0.102	1.09	0.98	1.21

Chr, chromosome; HWE, Hardy–Weinberg equilibrium; MAF, minor allele frequency; SNP, single nucleotide polymorphism.

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.[24] 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_{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_{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_{trend=}$0.009, $p_{trend=}$0.02 respectively, online supplementary table S2). In addition, the analysis reveals nominal association (p_{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 (*REL*, *PLCL2* and *STAT4*) the direction of the effect was opposite to that reported in the RA studies (figure 1).

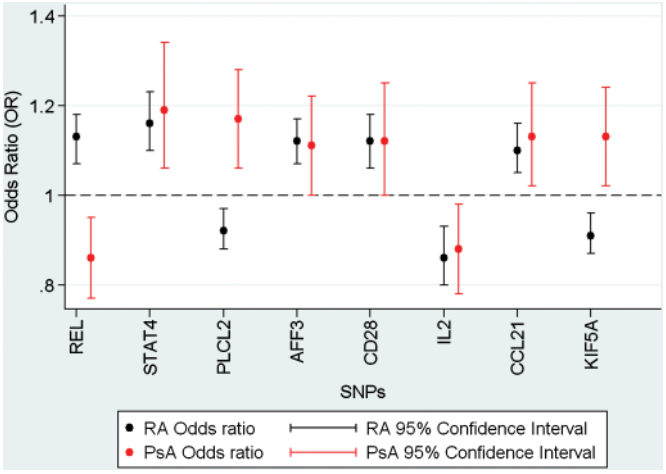

Figure 1 OR plots for eight SNPs demonstrating evidence for association to PsA susceptibility, highlighting the opposing direction of effects for *REL, PLCL2* and *KIF5A*. PsA, psoriatic arthritis; RA, rheumatoid arthritis, SNP, single nucleotide ploymorphism.

Subphenotype analysis revealed a greater effect for the *REL* SNP, rs13017599, in the late onset psoriasis (type II) and the seronegative 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.[2 3] 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.[25] Similarly, association at the *REL* locus SNP, rs13017599, has been reported previously in psoriasis but the opposite allele has also been associated with RA.[26 27] 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.[18 28–31] 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 NFκB 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).[27] 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.[1 15]

Of the other loci with nominal evidence for association, *STAT4* has been reported to be associated with psoriasis previously in a Greek population.[32] 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[33] and with the same SNP in a UK psoriasis cohort.[34]

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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Competing interests None.

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REFERENCES

1. **Stahl EA**, Raychaudhuri S, Remmers EF, *et al*. Genome-wide association study meta-analysis identifies seven new rheumatoid arthritis risk loci. *Nat Genet* 2010;**42**:508–14.
2. **Eyre S**, Hinks A, Bowes J, *et al*. Overlapping genetic susceptibility variants between three autoimmune disorders: rheumatoid arthritis, type 1 diabetes and coeliac disease. *Arthritis Res Ther* 2010;**12**:R175.
3. **Orozco G**, Eyre S, Hinks A, *et al*. Study of the common genetic background for rheumatoid arthritis and systemic lupus erythematosus. *Ann Rheum Dis* 2011;**70**:463–8.
4. **Ho PY**, Barton A, Worthington J, *et al.* Investigating the role of the HLA-Cw*06 and HLA-DRB1 genes in susceptibility to psoriatic arthritis: comparison with psoriasis and undifferentiated inflammatory arthritis. *Ann Rheum Dis* 2008;**67**:677–82.
5. **Hinks A**, Barton A, John S, *et al.* Association between the PTPN22 gene and rheumatoid arthritis and juvenile idiopathic arthritis in a UK population: further support that PTPN22 is an autoimmunity gene. *Arthritis Rheum* 2005;**52**:1694–9.
6. **Hüffmeier U**, Reis A, Steffens M, *et al.* Male restricted genetic association of variant R620W in PTPN22 with psoriatic arthritis. *J Invest Dermatol* 2006;**126**:932–5.
7. **Hüffmeier U**, Uebe S, Ekici AB, *et al.* Common variants at TRAF3IP2 are associated with susceptibility to psoriatic arthritis and psoriasis. *Nat Genet* 2010;**42**:996–9.
8. **Butt C**, Peddle L, Greenwood C, *et al.* Association of functional variants of PTPN22 and tp53 in psoriatic arthritis: a case-control study. *Arthritis Res Ther* 2006;**8**:R27.
9. **Ho P**, Bruce IN, Silman A, *et al.* Evidence for common genetic control in pathways of inflammation for Crohn's disease and psoriatic arthritis. *Arthritis Rheum* 2005;**52**:3596–602.
10. **Al-Heresh AM**, Proctor J, Jones SM, *et al.* Tumour necrosis factor-alpha polymorphism and the HLA-Cw*0602 allele in psoriatic arthritis. *Rheumatology (Oxford)* 2002;**41**:525–30.
11. **Balding J**, Kane D, Livingstone W, *et al.* Cytokine gene polymorphisms: association with psoriatic arthritis susceptibility and severity. *Arthritis Rheum* 2003;**48**:1408–13.

12. **Moll JM**, Wright V. Psoriatic arthritis. *Semin Arthritis Rheum* 1973;**3**:55–78.
13. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3000 shared controls. *Nature* 2007;**447**:661–78.
14. **Raychaudhuri S**, Remmers EF, Lee AT, *et al.* Common variants at CD40 and other loci confer risk of rheumatoid arthritis. *Nat Genet* 2008;**40**:1216–23.
15. **Raychaudhuri S**, Thomson BP, Remmers EF, *et al*. Genetic variants at CD28, PRDM1 and CD2/CD58 are associated with rheumatoid arthritis risk. *Nat Genet* 2009;**41**:1313–8.
16. **Barton A**, Eyre S, Ke X, *et al*. Identification of AF4/FMR2 family, member 3 (AFF3) as a novel rheumatoid arthritis susceptibility locus and confirmation of two further pan-autoimmune susceptibility genes. *Hum Mol Genet* 2009;**18**:2518–22.
17. **Barton A**, Thomson W, Ke X, *et al*. Rheumatoid arthritis susceptibility loci at chromosomes 10p15, 12q13 and 22q13. *Nat Genet* 2008;**40**:1156–9.
18. **Thomson W**, Barton A, Ke X, *et al*. Rheumatoid arthritis association at 6q23. *Nat Genet* 2007;**39**:1431–3.
19. **Plenge RM**, Cotsapas C, Davies L, *et al.* Two independent alleles at 6q23 associated with risk of rheumatoid arthritis. *Nat Genet* 2007;**39**:1477–82.
20. **Plenge RM**, Seielstad M, Padyukov L, *et al.* TRAF1-C5 as a risk locus for rheumatoid arthritis—a genomewide study. *N Engl J Med* 2007;**357**:1199–209.
21. **Remmers EF**, Plenge RM, Lee AT, *et al.* STAT4 and the risk of rheumatoid arthritis and systemic lupus erythematosus. *N Engl J Med* 2007;**357**:977–86.
22. **Zhernakova A**, Alizadeh BZ, Bevova M, *et al.* Novel association in chromosome 4q27 region with rheumatoid arthritis and confirmation of type 1 diabetes point to a general risk locus for autoimmune diseases. *Am J Hum Genet* 2007;**81**:1284–8.
23. **Plant D**, Flynn E, Mbarek H, *et al.* Investigation of potential non-HLA rheumatoid arthritis susceptibility loci in a European cohort increases the evidence for nine markers. *Ann Rheum Dis* 2010;**69**:1548–53.
24. **Purcell S**, Neale B, Todd-Brown K, *et al.* PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet* 2007;**81**:559–75.
25. **Barrett JC**, Hansoul S, Nicolae DL, *et al*. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. *Nat Genet* 2008;**40**:955–62.
26. **Gregersen PK**, Amos CI, Lee AT, *et al.* REL, encoding a member of the NF-kappaB family of transcription factors, is a newly defined risk locus for rheumatoid arthritis. *Nat Genet* 2009;**41**:820–3.
27. **Strange A**, Capon F, Spencer CC, *et al*. A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. *Nat Genet* 2010;**42**:985–90.
28. **Orozco G**, Hinks A, Eyre S, *et al*. Combined effects of three independent SNPs greatly increase the risk estimate for RA at 6q23. *Hum Mol Genet* 2009;**18**:2693–9.
29. **Musone SL**, Taylor KE, Lu TT, *et al.* Multiple polymorphisms in the TNFAIP3 region are independently associated with systemic lupus erythematosus. *Nat Genet* 2008;**40**:1062–4.
30. **Graham RR**, Cotsapas C, Davies L, *et al.* Genetic variants near TNFAIP3 on 6q23 are associated with systemic lupus erythematosus. *Nat Genet* 2008;**40**:1059–61.
31. **Nair RP**, Duffin KC, Helms C, *et al*. Genome-wide scan reveals association of psoriasis with IL-23 and NF-kappaB pathways. *Nat Genet* 2009;**41**:199–204.
32. **Zervou MI**, Goulielmos GN, Castro-Giner F, *et al.* STAT4 gene polymorphism is associated with psoriasis in the genetically homogeneous population of Crete, Greece. *Hum Immunol* 2009;**70**:738–41.
33. **Liu Y**, Helms C, Liao W, *et al.* A genome-wide association study of psoriasis and psoriatic arthritis identifies new disease loci. *PLoS Genet* 2008;**4**:e1000041.
34. **Warren RB**, Smith RL, Flynn E, *et al*. A systematic investigation of confirmed autoimmune loci in early-onset psoriasis reveals an association with IL2/IL21. *Br J Dermatol* 2011;**164**:660–4.