EXTENDED REPORT

Investigation of rheumatoid arthritis susceptibility loci in juvenile idiopathic arthritis confirms high degree of overlap

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ABSTRACT

Objectives Rheumatoid arthritis (RA) shares some similar clinical and pathological features with juvenile idiopathic arthritis (JIA); indeed, the strategy of investigating whether RA susceptibility loci also confer susceptibility to JIA has already proved highly successful in identifying novel JIA loci. A plethora of newly validated RA loci has been reported in the past year. Therefore, the aim of this study was to investigate these single nucleotide polymorphisms (SNP) to determine if they were also associated with JIA.

Methods Thirty-four SNP that showed validated association with RA and had not been investigated previously in the UK JIA cohort were genotyped in JIA cases (n=1242), healthy controls (n=4281), and data were extracted for approximately 5380 UK Caucasian controls from the Wellcome Trust Case–Control Consortium 2. Genotype and allele frequencies were compared between cases with JIA and controls using PLINK. A replication cohort of 813 JIA cases and 3058 controls from the USA was available for validation of any significant findings.

Results Thirteen SNP showed significant association (p<0.05) with JIA and for all but one the direction of association was the same as in RA. Of the eight loci that were tested, three showed significant association with RA loci has been reported in the past year. Therefore, the meantime, there are other approaches that can be used to identify genetic risk factors for JIA. We and other investigators have successfully exploited the fact that many complex autoimmune diseases share common genetic risk factors; for example, protein tyrosine phosphatase non-receptor 22 (PTPN22) and interleukin 2 receptor α (IL2RA) both confer susceptibility to multiple autoimmune diseases, such as type 1 diabetes (T1DM), rheumatoid arthritis (RA) and autoimmune thyroid disease, and markers in both these genes have been associated with JIA.4 Of the autoimmune diseases, RA shares the most similar clinical and pathological features with JIA, and we have previously reported considerable overlap in genetic susceptibility loci for the two diseases, finding evidence of association for four loci (STAT4, TRAF1/C5, TNFAIP3 and PRKCQ) with JIA.7 The first three of which have further evidence of association with JIA in independent cohorts.5 9 In the past few years many additional RA loci have been identified10–12 and these represent excellent candidate JIA loci. Therefore the aim of this study was to investigate whether newly identified RA susceptibility loci also confer susceptibility to JIA.

MATERIALS AND METHODS

SNP selection

Single-nucleotide polymorphisms (SNP) that showed validated association with RA and had not been investigated previously in the UK JIA cohort were selected for genotyping. These were identified from three recent RA publications.10–12 The first was a GWAS in cases and controls from North America and from that study SNP in REL (rs13031237), BLK (rs2736340) and CTLA4 (rs231755) were selected for genotyping.10 The second was a meta-analysis of published GWAS in which 13 novel RA SNP were identified.11 Finally, a second larger meta-

Juvenile idiopathic arthritis (JIA) is a collective term that encompasses all forms of arthritis, with an unknown cause, that have an onset before the age of 16 years and that persist for more than 6 weeks.1 There are seven disease categories as defined by the International League of Associations for Rheumatology (ILAR) classification criteria and, while there is heterogeneity between the subtypes in terms of disease presentation, clinical symptoms and prognosis, they do appear to share genetic susceptibility risk factors.3 4 JIA is a relatively rare disease and as such it has taken longer to collect the large and appropriately powered sample sizes required for genome-wide association studies (GWAS). International collaborations have been established and GWAS for JIA have been performed or are in progress.5 However, in the meantime, there are other approaches that can
analysis of RA cases and controls identified a further 21 SNP with replicated association with RA. Of these, 10 had achieved genome-wide significance in the combined analysis and 11 had highly suggestive evidence of association although not exceeding the threshold for claims of genome-wide significance. Results for three of these SNP (in IL2RA, AFF3 and cI2orf30) had previously been investigated in the UK JIA cohort, and so were not included in this study. In total, therefore, 34 SNP were selected for genotyping.

Subjects

UK cohort
DNA was available for 1242 UK Caucasian JIA patients from three sources: The British Society for Paediatric and Adolescent Rheumatology national repository of JIA (n=654); a group of UK Caucasian patients with long-standing JIA (n=201), described previously, and a third cohort collected as part of the Childhood Arthritis Prospective Study, a prospective inception cohort study of JIA cases from five centres across the UK (n=587). JIA cases were classified according to ILAR criteria (see supplementary table 1, available online only). Healthy Caucasian control DNA samples (n=4281) were available from five centres in the UK, collected as part of the UK RA genetics (UKRAG) consortium, as described previously. All individuals were recruited with ethics approval and provided informed consent (North-West Multi-Centre Research Ethics Committee (MREC 99/8/84) and the University of Manchester Committee on the Ethics of Research on Human Beings). Additional control genotyping data were extracted from the Wellcome Trust Case-Control Consortium (WTCCC2) European Genome-Phenome Archive website (http://www.ebi.ac.uk/ega/). SNP had been genotyped on either the Illumina (n=5200) or Affymetrix (n=5380) platform. If a SNP had been genotyped on both platforms then the results from the analysis with the larger control set was presented.

All SNP were genotyped in the UK JIA cases using the Sequenom MassARRAY platform according to manufacturer’s instructions (Sequenom, San Diego, California, USA; http://www.sequenom.com/). A 90% sample quality control rate and 90% genotyping success rate was imposed.

US cohort
For validation of the findings in the UK cohort, genotype information was available from a cohort of 813 JIA cases and 3058 controls from the USA. These data are from a GWAS, which has previously been investigated for autoimmune overlap. For the JIA children, with polyarticular (rheumatoid factor negative) and oligoarticular JIA, approximately 95% of the cases were recruited at the Cincinnati Children’s Hospital Medical Center (CCHMC) or as part of a National Institute of Arthritis and Musculoskeletal and Skin Diseases-supported JIA affected sibpair registry. The remaining cases were contributed by collaborating centres that included the Children’s Hospital of Wisconsin, Schneider Children’s Hospital and Children’s Hospital of Philadelphia. JIA cases were classified according to ILAR criteria and comprised cases from three subtypes of JIA (see supplementary table 1, available online only). The control cohort (n=3058) comprised 658 healthy children aged between 3 and 18 years, recruited from the general population to represent the geographical region served by CCHMC. In addition, 2400 healthy controls of European ancestry were genotyped at the Broad Institute on the Affymetrix SNP array 6.0, which have been collected as part of the Molecular Genetics of Schizophrenia GWAS. Both cases and controls were subjected to principal component analysis, and any outliers were excluded from analysis. SNP were genotyped using the Affymetrix genome-wide human SNP array 6.0. The study had full ethics committee approval (CCHMC Institutional Review Board) and was fully compliant with the Declaration of Helsinki.

Statistical analysis
Power calculations were performed using QUANTO to calculate the prior probability of detecting association in the current UK sample size at the allele frequency and effect sizes reported previously in RA. Calculations assumed a log-additive model and an α value of 0.05. Power calculations were also performed to determine the power of the US cohort to validate the findings of the UK cohort. Genotype and allele frequencies were compared between cases with JIA and controls using the Cochran–Armitage trend test implemented in PLINK and allelic OR and their 95% CI were calculated.

Analysis was performed in all JIA cases for the UK cohort initially but then the analysis was restricted to subtypes equivalent to those in the US cohort (see supplementary table 1, available online only) to allow for comparison of OR and for combining the data in a meta-analysis.

RESULTS

The JIA case number after quality control was 1229. The power calculation for each SNP is shown in supplementary table 3 (available online only).

Of the 34 SNP selected for genotyping, four failed to genotype (rs892188 (ICAM1), rs934754 (SPRED2), rs7155608 (BAX) and rs840016 (CD247), although a SNP in the CD247 gene identified in the Raychaudhuri study was genotyped, rs77735860, which has r=0.68 with rs840016. Therefore, there were 30 SNP for analysis. The SNP in IRF5 (rs10486561) failed genotyping in the UKRAG control dataset, therefore the comparison was limited to the WTCCC2 control data while conversely the SNP in TACAP (rs934851) failed to genotype in the WTCCC2 control cohort so the comparison was limited to the UKRAG control dataset.

Thirteen SNP showed nominal evidence of association with JIA (p<0.05) (table 1). Results for all SNP are provided in supplementary table 2 (available online only). Figure 1 shows a comparison between the association analysis results in RA and JIA. For all but one (NHLH2) of the 13 loci the direction of association was the same as that observed in the RA studies, with similar OR and sometimes stronger effect sizes in JIA (figure 1).

Of the 13 loci that showed nominal association with JIA in our UK cohort, eight had genotype data available in the US validation cohort (table 2). There were no data for the IL2, ANKRD55, C5orf30 or the IRF5 SNP. Of the eight SNP, three (rs77735860 in CD247, rs706777 in IL2RA and rs7254029 in PTPN2) showed association with JIA in the US cohort, and meta-analysis of the two cohorts strengthened the association.

DISCUSSION

The now well-established overlap of genetic susceptibility risk factors across quite clinically and phenotypically different autoimmune diseases has been an exciting discovery that has emerged from the GWAS era. It suggests there will be shared pathogenic pathways and the potential for shared therapies for these diseases. Furthermore, it can be exploited as a strategy for the identification of novel risk factors for related autoimmune diseases, including JIA. There is already compelling evidence that many susceptibility loci are shared between RA and JIA (PTPN22, PTPN21, IL2RA, STAT4, IL2, TRAF1/C5).
Table 1 RA-associated SNP nominally associated with JIA (all JIA subtypes) (p<0.05)

| SNP          | CHR | Position | Gene       | Minor allele | Major allele | MAF cases | MAF controls | HWE controls | Case 1 (%) | Case 12 (%) | Case 22 (%) | Control 11 (%) | Control 12 (%) | Control 22 (%) | pTREND | OR 95% CI |
|--------------|-----|----------|------------|--------------|--------------|-----------|--------------|--------------|------------|-------------|-------------|----------------|----------------|----------------|--------|-----------|
| rs4272626    | 1   | 11149950 | NNLH2      | T            | C            | 0.34      | 0.36         | 0.79         | 517 (44.2) | 511 (43.7)  | 142 (12.1)  | 3264 (40.8)   | 3702 (46.3)   | 1035 (12.9)    | 0.05   | 0.91 (0.83 to 1.00) |
| rs1586238    | 1   | 11706461 | CD4        | G            | C            | 0.26      | 0.24         | 0.48         | 636 (54.4) | 455 (39.8)  | 79 (6.8)    | 4586 (573)    | 2957 (37.0)   | 456 (5.7)      | 0.03   | 1.11 (1.01 to 1.23) |
| rs7173960    | 1   | 16968139 | CD247      | G            | A            | 0.38      | 0.42         | 0.62         | 456 (39.2) | 520 (44.7)  | 187 (16.1)  | 2652 (33.4)   | 3949 (48.5)   | 1443 (18.2)    | 0.0003 | 0.85 (0.78 to 0.93) |
| rs10919563   | 1   | 19697065 | PTTPC      | A            | G            | 0.09      | 0.13         | 0.92         | 917 (73.0) | 171 (15.5)  | 17 (1.5)    | 5934 (75.3)   | 1824 (22.9)   | 137 (1.7)      | 2.57×10⁻⁷ | 0.67 (0.58 to 0.78) |
| rs874040     | 4   | 25717292 | RBPU       | G            | A            | 0.33      | 0.30         | 0.62         | 445 (34.4) | 451 (45.0)  | 107 (10.7)  | 3938 (48.8)   | 3401 (42.0)   | 754 (9.3)      | 0.01   | 1.14 (1.03 to 1.26) |
| rs13119723   | 4   | 12343763 | IL2, IL21  | A            | G            | 0.13      | 0.16         | 0.24         | 721 (60.6) | 204 (17.5)  | 24 (2.5)    | 5631 (71.0)   | 2090 (26.3)   | 214 (2.7)      | 0.004  | 0.8 (0.71 to 0.93)  |
| rs10043027*  | 5   | 55470977 | ANKRD55    | A            | G            | 0.09      | 0.11         | 0.20         | 825 (64.2) | 167 (17.6)  | 9 (0.9)     | 6171 (79.1)   | 1583 (19.5)   | 112 (1.4)      | 0.01   | 0.81 (0.69 to 0.95)  |
| rs26235      | 5   | 10262461 | NNLH2      | T            | C            | 0.29      | 0.33         | 0.57         | 506 (50.4) | 417 (41.6)  | 80 (8.0)    | 3579 (45.0)   | 3536 (44.5)   | 831 (10.5)     | 0.0003 | 0.83 (0.75 to 0.92)  |
| rs10488631   | 5   | 12807480 | IRF5       | T            | C            | 0.13      | 0.11         | 0.47         | 902 (76.5) | 257 (21.8)  | 17 (1.5)    | 4119 (79.6)   | 1003 (19.4)   | 54 (1.0)       | 0.009  | 1.2 (1.05 to 1.37)  |
| rs273630     | 8   | 11381382 | BLK        | T            | C            | 0.27      | 0.24         | 0.51         | 522 (42.0) | 406 (40.8)  | 68 (6.8)    | 4631 (67.1)   | 3002 (42.0)   | 481 (6.5)      | 0.006  | 1.16 (1.04 to 1.28) |
| rs706778     | 10  | 6138955  | IL2RA      | T            | C            | 0.45      | 0.40         | 0.80         | 314 (31.4) | 479 (47.9)  | 208 (20.8)  | 2926 (36.1)   | 3883 (47.9)   | 1304 (16.1)    | 5.16×10⁻⁵ | 1.21 (1.09 to 1.33) |
| rs2872507    | 17  | 35294298 | ORMOL3     | G            | A            | 0.52      | 0.48         | 0.75         | 221 (23.2) | 474 (48.8)  | 256 (26.9)  | 2199 (27.3)   | 4001 (49.7)   | 1846 (22.9)    | 0.0009 | 1.18 (1.07 to 1.29) |
| rs7234029    | 18  | 12807080 | PTPN2      | G            | A            | 0.19      | 0.16         | 0.33         | 766 (65.5) | 42 (3.6)    | 42 (3.6)    | 566 (71.1)    | 2127 (26.6)   | 182 (2.3)      | 1.25×10⁻⁵ | 1.18 (1.15 to 1.43) |

**r²=0.86 with rs6859219 the single-nucleotide polymorphism (SNP) genotyped in the study by Stahl et al.**

Case 11, case genotype counts and percentage of major allele homozygotes; Case 12, case genotype counts and percentage of heterozygotes; Case 22, case genotype counts and percentage of minor allele homozygotes; Control 11, control genotype counts and percentage of major allele homozygotes; Control 12, control genotype counts and percentage of heterozygotes; Control 22, control genotype counts and percentage of minor allele homozygotes; p value for deviation from HWE, CHR, chromosome; HWE, Hardy-Weinberg equilibrium; JIA, juvenile idiopathic arthritis; MAF, minor allele frequency; pTREND, p value for the Armitage test for trend as generated in PLINK; RA, rheumatoid arthritis.

The novel SNP associated here is in only one of the genes. The other SNP are associated in other diseases. The SNP associated here is in only one of the genes.
### Table 2: Analysis of all JIA nominally associated SNP in oligoarthritis and polyarthritis subtypes in UK discovery cohort, the US validation cohort and combined meta-analysis

| SNP          | Chr Position | MAF cases | OR (95% CI) | Combined meta-analysis p value |
|--------------|--------------|-----------|-------------|--------------------------------|
| rs2104286    | 12q11.1        | 0.16     | 9.3×10⁻⁶    |                                |
| rs706778     | 12q11.1        | 0.16     | 1.48 (1.29 to 1.69) |                                |
| rs11586238   | 1p32           | 0.33     | 8.1×10⁻¹³   |                                |
| rs706778     | 1q42.11        | 0.23     | 1.41 (1.28 to 1.55) |                                |
| rs10919563   | 1q42.11        | 0.09     | 3.3×10⁻⁶    |                                |
| rs4272626    | 1q42.11        | 0.16     | 1.16 (0.98 to 1.36) |                                |
| rs874040     | 1q42.11        | 0.04     | 1.09 (1.01 to 1.18) |                                |
| rs2736340    | 1q42.11        | 0.26     | 3.3×10⁻⁶    |                                |
| rs706778     | 1q42.11        | 0.05     | 1.08 (1.0 to 1.19) |                                |
| rs706778     | 1q42.11        | 0.06     | 1.09 (1.01 to 1.18) |                                |
| rs10919563   | 1q42.11        | 0.31     | 1.08 (1.0 to 1.19) |                                |
| rs706778     | 1q42.11        | 0.02     | 1.09 (1.01 to 1.18) |                                |
| rs613855     | 1q42.11        | 0.02     | 1.09 (1.01 to 1.18) |                                |
| rs2872507    | 1q42.11        | 0.01     | 1.09 (1.01 to 1.18) |                                |

Chr, chromosome; JIA, juvenile idiopathic arthritis; MAF, minor allele frequency; pTREND, p value for the Armitage test for trend as generated in PLINK; SNP, single-nucleotide polymorphism.

The JIA association findings were not validated in the US cohort for CD2, RBPF1, BLK and ORMDL3, and only ORMDL3 remained significant in the combined analysis. The US cohort was underpowered to detect an effect with all of these loci apart from ORMDL3 (see supplementary table 3, available online only), therefore further validation is needed.

In addition it should be noted that for the 16 SNP that were not significantly associated with JIA in this study, we had between 29% and 99% power to detect an association; therefore, for some of these SNP, larger datasets and meta-analyses will be required to exclude association with JIA completely.

JIA is a heterogeneous disease and it may be expected that there are genetic differences across the JIA subtypes and some subtype-specific effects have been identified. In this study our strategy was to look for shared autoimmune or inflammatory arthritis susceptibility loci, and it would be interesting to investigate whether these associations are common to all JIA subtypes or are restricted to some subtypes. However, stratified analysis leads to small sample sizes for many of the subtypes and further issues with multiple testing. Larger cohorts of the ILAR subtypes are required to improve the power to detect any subtype-specific effects. We have stratified our analysis just to investigate the oligoarthritis and rheumatoid factor-negative polyarthritis subtypes as these were the subtypes comprising the validation cohort.

For all these loci identified for JIA we have only tested one SNP, the SNP most significantly associated with RA from GWAS. In most cases for the genes identified to date for RA and other autoimmune diseases, the actual causal variant has yet to be identified, which may reduce the power of this study even further, so further fine-mapping of the genes/regions is now required.

In conclusion, the strategy of testing loci identified in other autoimmune diseases, such as RA, for association with JIA is proving successful in the identification of novel JIA loci and is a complementary approach to the hypothesis-free methods of GWAS. In the past few years we have investigated 45 loci that confer susceptibility to RA for association with JIA.
Of these, 22 show association (p<0.05) with JIA in our UK cohort and 11 of these show validated association with JIA in independent cohorts. Clearly, there is a selection bias given the strategy used to select SNP to test; however, there still remains quite considerable overlap between two distinct clinical entities. Many of these loci also confer susceptibility to other autoimmune diseases and may thus represent genes controlling general immune function, the defects of which may lead to an enhanced autoimmune response. Despite the success of this approach in identifying novel JIA loci, large well-powered GWAS will be required to identify disease-specific loci for JIA and its subtypes.

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