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 in the US cohort.

Conclusions A novel JIA susceptibility locus was identified, CD247, which represents another JIA susceptibility gene whose protein product is important in T-cell activation and signalling. The authors have also confirmed association of the PTPN2 and IL2RA genes with JIA, both reaching genome-wide significance in the combined analysis.

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 criteria2 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 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 6 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 PRKCC) with JIA.7 The first three of which have further evidence of association with JIA in independent cohorts.8 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 (rs231753) 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-
Clinical and epidemiological research

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 \textit{IL2RA}, \textit{AFF3} and \textit{c12orf30}) 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 2 (WTCCC2) European Genome–Phenome Archive website (http://www.ebi.ac.uk/ega/). SNP had been genotyped on either the Illumina (n=5200) or Affymetrix platform according to manufacturer’s instructions (Sequenom, San Diego, California, USA; http://www.sequenom.com/). A 90% sample quality control 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 \( \alpha \) 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 Cochrane–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, rs934734, rs7155608, and rs840016), although a SNP in the \textit{CD247} gene identified in the Raychaudhuri study was genotyped, which has \( r^2=0.68 \) with rs840016. Therefore, there were 30 SNP for analysis. The SNP in \textit{IRF5} (rs10485631) failed genotyping in the UKRAG control dataset, therefore the comparison was limited to the WTCCC2 control data while conversely the SNP in \textit{TAGAP} (rs594581) 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 (\textit{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 \textit{IL2, ANKRD55, C5orf30} or the \textit{IRF5} SNP. Of the eight SNP, three (rs1773560 in \textit{CD247}, rs706778 in \textit{IL2RA} and rs7234029 in \textit{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 previously investigated in the UK JIA cohort.
Table 1  RA-associated SNP nominally associated with JIA (all JIA subtypes) (p<0.05)

<table>
<thead>
<tr>
<th>SNP</th>
<th>CHR</th>
<th>Position</th>
<th>Gene</th>
<th>MAF cases</th>
<th>Major allele</th>
<th>Minor allele</th>
<th>OR</th>
<th>95% CI</th>
<th>pTREND</th>
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<td>112816850</td>
<td>CD2</td>
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<td>0.24</td>
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<td>0.03</td>
<td>1.01 to 1.00</td>
<td>0.003</td>
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<td>CD247</td>
<td>0.38</td>
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<td>0.85 (0.78 to 0.93)</td>
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<td>1</td>
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<td>0.13</td>
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<td>ANKRD55</td>
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<td>0.11</td>
<td>0.20</td>
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<td>0.0009</td>
<td>0.82 (0.71 to 0.95)</td>
<td>0.002</td>
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</table>

Figure 1  Plot of OR for minor allele for 13 loci showing nominal evidence of association with juvenile idiopathic arthritis (JIA), comparison with rheumatoid arthritis (RA). Odds ratios obtained from Raychaudhuri et al., Stahl et al., and Gregersen et al.

Amongst others. In this study we have identified and validated association with three novel loci, originally associated with RA.

One of these identifies a new JIA susceptibility gene, CD247, a good candidate for JIA as it encodes the zeta chain of the T-cell receptor–CD3 complex and adds another gene to the list of JIA susceptibility loci that play a role in T-cell activation and signaling (PTPN22, IL2RA, PTPN2, SH2B3 and STAT4). In addition to the reported associations with RA, SNP within CD247 have also been associated with coeliac disease and with systemic sclerosis. The JIA-associated SNP is in complete linkage disequilibrium (LD) (r²=1) with the SNP associated with systemic sclerosis (rs2056626) and in strong LD (r²=0.86) with the SNP most significantly associated with coeliac disease (rs864537). The risk variant of the SNP has also been correlated with cis gene expression of CD247.

We found strong evidence for association of a SNP, rs7234029, in the protein tyrosine phosphatase non-receptor 2 (PTPN2) gene with JIA in our UK cohort. There is already replicated evidence for association of SNP within this gene with JIA in US and German cohorts. In the US study, the SNP with the strongest association was also rs7234029, and it reached genome-wide levels of significance; in addition there was association with four additional SNP. Meta-analysis of the UK JIA cohort study with the US data further established PTPN2 as an important JIA susceptibility locus (combined p value 8.1×10⁻¹³). The PTPN2 gene has been associated with multiple autoimmune diseases, including T1DM, Graves’ disease, Crohn’s disease and coeliac disease. In T1DM, fine-mapping suggests there are two independently associated SNP, rs45450798 and rs478582. These SNP are only in modest LD with rs7234029. Further fine-mapping of the gene in RA and JIA will be required to identify the causal variant, whether there are multiple independent effects and whether the associations are the same across the different autoimmune diseases. PTPN2 encodes a protein tyrosine phosphatase, similar to PTPN22, which also plays a role in the activation and regulation of T and B cells.

SNP within IL2RA have previously been shown to be associated with JIA using these same UK and US cohorts as well as many other autoimmune diseases such as RA, T1DM and multiple sclerosis, but the association is complex with multiple independent effects and different associations across different diseases. The novel SNP associated here is in only
In the initial analysis of the UK cohort only the most significant association was for a SNP in the protein-tyrosine phosphatase receptor type C (PTPRC) gene, which again is a promising candidate gene. This gene encodes the common leucocyte antigen, CD45, which is a haemopoietic cell-specific tyrosine phosphatase. CD45 is essential for the activation of T and B cells by mediating cell-to-cell contacts and regulating protein-tyrosine kinases involved in signal transduction.\(^{30}\) However, this was not validated in the US cohort; in fact, there was a trend towards an association but in the opposite direction. There are a number of possible reasons for this, including a false positive in the initial UK dataset, a false negative in the US dataset, unrecognised population stratification, phenotypic heterogeneity and different environmental exposures. Analysis of this SNP in additional larger cohorts is required to confirm or refute association with this locus.

The JIA association findings were not validated in the US cohort for CD2, RBPJ, BLK and ORMDL3, and only ORMDL3 remained significant in the combined analysis. The US cohort was underpowered to detect an effect with all 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.\(^{31,32}\) 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.\(^{7,13,33}\)

### Table 2

<table>
<thead>
<tr>
<th>SNP</th>
<th>Chr Position</th>
<th>Chr</th>
<th>Position</th>
<th>OR (95% CI)</th>
<th>MAF cases</th>
<th>Combined meta-analysis p value</th>
<th>Breslow–Day p value</th>
<th>pTREND</th>
<th>MAF controls</th>
<th>Combined meta-analysis p value</th>
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<td>25717295</td>
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<td>1.09 (1.01 to 1.19)</td>
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The JIA association findings were not validated in the US cohort for CD2, RBPJ, BLK and ORMDL3, and only ORMDL3 remained significant in the combined analysis. The US cohort was underpowered to detect an effect with all these loci apart from ORMDL3 (see supplementary table 3, available online only), therefore further validation is needed.

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GWAS will be required to identify disease-specific loci for JIA to an enhanced autoimmune response. Despite the success of general immune function, the defects of which may lead remains quite considerable overlap between two distinct clinical given the strategy used to select SNP to test; however, there still still require to identify disease-specific loci for JIA and its subtypes.

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Patient consent Obtained.

Competing interests None.

Provenance and peer review Not commissioned, externally peer reviewed.

REFERENCES

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