No evidence that genetic predictors of susceptibility predict changes in core outcomes in JIA

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Abstract

Objectives. The clinical progression of JIA is unpredictable. Knowing who will develop severe disease could facilitate rapid intensification of therapies. We use genetic variants conferring susceptibility to JIA to predict disease outcome measures.

Methods. A total of 713 JIA patients with genotype data and core outcome variables (COVs) at diagnosis (baseline) and 1 year follow-up were identified from the Childhood Arthritis Prospective Study (CAPS). A weighted genetic risk score (GRS) was generated, including all single nucleotide polymorphisms (SNPs) previously associated with JIA susceptibility ($P$-value $<5\times10^{-08}$). We used multivariable linear regression to test the GRS for association with COVS (limited joint count, active joint count, physician global assessment, parent/patient general evaluation, childhood HAQ and ESR) at baseline and change in COVS from baseline to 1 year, adjusting for baseline COV and International League of Associations of Rheumatology (ILAR) category. The GRS was split into quintiles to identify high (quintile 5) and low (quintile 1) risk groups.

Results. Patients in the high-risk group for the GRS had a younger age at presentation (median low risk 7.79, median high risk 3.51). No association was observed between the GRS and any outcome measures at 1 year follow-up or baseline.

Conclusion. For the first time we have used all known JIA genetic susceptibility loci ($P$-value $<5\times10^{-08}$) in a GRS to predict changes in disease outcome measured over time. Genetic susceptibility variants are poor predictors of changes in core outcome measures, it is likely that genetic factors predicting disease outcome are independent to those predicting susceptibility. The next step will be to conduct a genome-wide association analysis of JIA outcome.

Key words: JIA, genetics, disease outcome

Rheumatology key messages

- A genetic risk score of JIA susceptibility variants is not associated with disease outcome at 1 year.
- Genetic predictors of JIA outcome are likely to be independent of susceptibility variants.
- A GWAS of JIA outcome is required to identify true genetic predictors of outcome.

*See supplementary data available at Rheumatology online for a list of the Childhood Arthritis Prospective Study (CAPS) Group members.
Introduction

JIA is the most common inflammatory rheumatic condition in children and young people (CYP) under 16 years of age, affecting ~12,000 CYP in the UK. JIA is an umbrella term that encompasses a group of conditions characterized by inflammatory arthritis and are classified by the ILAR classification system [1]. ILAR classification uses clinical and laboratory features to identify clinically homogeneous groups of patients. However, the clinical progression of JIA is unpredictable with patients often experiencing differing symptoms and varying prognosis [2]. Some patients may experience mild and short periods of inflammation in a single joint, whereas others can experience long-lasting inflammation in multiple joints, which can lead to joint damage/destruction and long-term disability. However, remission is achievable with the use of medication, and outcome of disease has significantly improved since the introduction of biologic therapies. Despite within-group heterogeneity, the best current predictor of outcome in JIA is ILAR category, where patients with oligoarthritis have been shown to have increased rates of inactive disease/remission, while patients with RF-positive polyarthritis have the poorest outcomes [3, 4]. Age at onset and sex have also been associated with achieving clinically inactive disease/remission, with younger age at onset being associated with more severe disease and a decreased chance of inactive disease [5, 6], and female sex associated with higher levels of physical disability [6], although these associations are not often evident after adjusting for ILAR [7].

A range of therapies are now available to clinicians to treat JIA, including NSAIDs, steroids, intra-articular steroid injections, conventional synthetic DMARDs such as MTX, as well as biological DMARDs such as etanercept and adalimumab. There is evidence that early treatment within a so-called ‘window of opportunity’ may be associated with better outcomes [8]. A delay between symptom onset and treatment with MTX has been associated with reduced treatment response [9, 10] and the same has been observed with etanercept [11]. Studies have also shown a high response rate and higher rates of clinically inactive disease using early aggressive treatment including biologics [12, 13]. This is of particular importance as treatment with biologic therapies is often reserved for later in the disease course when patients have failed treatment with conventional DMARDs, suggesting that by this point the ‘window of opportunity’ may have passed.

The increasing array of treatment options alongside limited predictors of treatment response and poor outcomes makes the clinician’s choice of therapy a difficult one. Clinicians must balance the need for appropriately aggressive therapies for some with the risk of overtreatment for others. The lack of clinical predictors of inflammatory outcome means that few prediction models exist and those that do generally perform poorly [7, 9, 14]. It is hoped that the addition of biological markers of disease such as serum protein levels and genetic variants will improve the prediction of outcome. If we could predict which CYP will have poorer outcome they may be able to be fast tracked to a more aggressive treatment strategy, including earlier introduction of biologic therapy, allowing clinicians to make the most of the ‘window of opportunity’, improving overall outcomes, reducing long-term damage/disability and in turn the economic burden of disease [2, 15, 16].

There have been efforts to standardize criteria for the evaluation of patient outcome, with the validation of six core outcome variables (COVs) [17]: physicians global assessments (PGA) of overall disease activity; patient/parent assessment of overall well-being; number of joints with active arthritis; number of joints with limitation in motion; functional ability [e.g. validated translation of childhood HAQ (CHAQ)]; and an index of inflammation (either ESR or CRP). This led to the development of the Juvenile Arthritis Disease Activity Scores (JADAS), which incorporates four measures: PGA; parent/patient global assessment of well-being; a count of joints with active disease; and ESR [17, 18].

Efforts to identify genetic variants that predict disease outcome have been hampered by the lack of large datasets; therefore, few studies have been carried out. A study in 2003 looked at a cohort of 316 patients and found that persistent disease was predicted by the presence of HLA-DRB1*08; joint erosions were predicted by symmetric arthritis in addition to HLA-DRB1*08 and HLA-B27 in combination with HLA-DRB1*04 was a predictor of joint erosions in oligoarticular JIA [6]. A study of Portuguese JIA patients investigated single nucleotide polymorphisms (SNPs) associated with JIA susceptibility and genes with known function in the immune system [19]. A univariable analysis found significant associations between poor prognosis for allele A of rs6920220 (TNFAIP3), allele G of rs3761847 (TRAFL/C5) and allele G of rs7234029 (PTPN2), where poor prognosis was defined as CHAQ/HAQ >0.75 at the last visit and/or treatment with biological therapy. However, in multivariable analysis, none of the genetic associations withstood correction for multiple testing.

In contrast to the search for predictors of outcome, the search for JIA susceptibility variants has been extremely successful [20–22], identifying 24 SNPs associated with risk of disease at genome wide significance. However, many of the JIA susceptibility variants identified confer small effect sizes and therefore explain a small proportion of the heritability, as is the case in many complex phenotypes. One way to overcome the issue of power due to sample size limitations and small effect sizes is to use genetic risk scores (GRS), which combine the effects of multiple genetic variants into a single predictor. Combining risk alleles of selected SNPs into an aggregate GRS reduces the need to correct for multiple testing and allows a multigenic assessment of risk and can increase power to detect and overall effect [23–26]. Here for the first time we have used our existing knowledge of disease susceptibility to see if a GRS
composed of these variants can be used to predict disease outcome.

**Patients and methods**

**Study population**

This analysis includes CYP recruited to the Childhood Arthritis Prospective Study (CAPS), a prospective inception cohort recruiting from seven UK centres since 2001. Details of this cohort have been described previously [27]. CAPS was approved by the Northwest Multicentre Research Ethics Committee (NREC 02/8/104) and written informed consent from parents/guardians and where appropriate from participants was obtained.

In this analysis, CYP were included if they had a physician’s diagnosis of JIA, categorised according to the ILAR classification, and were recruited to CAPS prior to 1 September 2017 (allowing at least 1 year follow-up), and had high-quality genotype data available. Patients with no ILAR category recorded were excluded. ILAR category was collected from the 1-year assessment to allow for categorization of persistent/extended oligoarthritis and for categories with extra-articular features ankylosing spondylitis; call rate $<0.98$ and discrepancy between genetically inferred sex and database records. SNPs that were non-autosomal, had call rate $<0.98$ or minor allele frequency $<0.01$ were excluded. Imputation was performed in the Michigan Imputation server using SHAPEIT2 and Minimac3, and the HaploType Reference Consortium reference panel. Following imputation SNPs were excluded based on minor allele frequency (MAF) $<0.01$ and imputation quality (r2) $<0.4$. For more information, see López-Isaac et al. [22].

**SNP genotyping**

Genotyping was carried out using the Illumina Infinium CoreExome and Infinium OmniExpress genotyping arrays as described in [22]. Briefly, sample level quality control was applied using the following exclusion criteria: call rate $<0.98$ and discrepancy between genetically inferred sex and database records. SNPs that were non-autosomal, had call rate $<0.98$ or minor allele frequency $<0.01$ were excluded. Imputation was performed in the Michigan Imputation server using SHAPEIT2 and Minimac3, and the HaploType Reference Consortium reference panel. Following imputation SNPs were excluded based on minor allele frequency (MAF) $<0.01$ and imputation quality (r2) $<0.4$. For more information, see López-Isaac et al. [22].

**Genetic risk score (GRS)**

Twenty-four SNPs previously associated with JIA susceptibility at genome-wide significance level ($P$-value $<5 \times 10^{-8}$) were selected for inclusion in the GRS [20–22] (Supplementary Table S1, available at Rheumatology online); two HLA SNPs and 22 non-MHC risk SNPs. In STATA v14, data were coded by carriage of the JIA risk allele (0,1,2). Each SNP was then weighted by the beta coefficient (natural log-odds ratio) for susceptibility from the most recent genome-wide association study (GWAS) [22]. Risk alleles and beta coefficients used can be found in Supplementary Table S2, available at Rheumatology online. A GRS score was then generated by summing over the 24 SNPs. Using a weighted risk score is important as it takes into account regions that have a stronger predictive relationship with JIA (such as PTPN22) as compared with the more recently discovered SNPs.

Six SNPs out of the 24 were reported in both the Immunochip and GWAS studies (PTPN22, STAT4, ANKRD55, ATXN2, PTPN2 and TYK2). For PTPN22 and TYK2, the same SNP was reported in both studies. For the remaining four SNPs, different SNPs were reported. In these cases, we used the SNP reported in the latest GWAS as the population was more homogeneous (UK vs US/UK/German) and were imputed to the latest reference panel. In order to test for potential bias caused by a lack of independence between the discovery cohort (most recent GWAS in which the beta coefficients were generated [22]) and this test cohort, we removed overlapping samples from the discovery cohort and redefined the weights (beta coefficients). The beta coefficients from the discovery cohort were then compared with the newly defined beta coefficients using a scatterplot.

The GRS was then split into quintiles to identify high (quintile 5) and low (quintile 1) risk groups. This allowed analysis of the two extremes of the GRS as well as analysis of the continuous GRS score.

**Outcome assessment**

Our primary analyses considered change in the COVs (active and limited joint counts, physician’s global assessment, parent global assessment, CHAQ and ESR from baseline to 1 year). As a secondary analyses, we also considered COVs at baseline.

The COVs were selected as they are routinely collected in clinic, and they make up the basis of the ACRpedi and the JADAS [18]. The individual components of these composite scores do not always correlate, therefore we have chosen to use the individual COVs to better reflect disease activity [2].

**Data collection**

Baseline data was collected at the point of first presentation to a paediatric or adolescent rheumatology clinic at one of seven centres across the UK and annually thereafter for 5 years. At each visit, patients (over age of 11 if they wish) or guardians were asked to complete a series of patient-reported outcome measures including the CHAQ. The CHAQ score totals 24 and is divided so that the final range is 0–3, with higher scores indicating poorer functional ability. Patients or guardians also complete a 100 mm pain visual analogue scale (VAS). Data from case notes also included ILAR category, the number of active and limited joints, the physician global assessment score and results of laboratory investigations including ESR (mm/h).

**Statistical analysis**

Missing outcome data (age at first presentation, age at onset, active joint count, limited joint count, physician
global assessment, parent global assessment, CHAQ, ESR and all change variables) were imputed over 20 imputations using multiple imputation by chained equations in STATA version 14.0 [28]; assuming data was missing at random.

Association of the GRS with change in COVs (or baseline COVs) was assessed via multivariable linear regression, through pooling models built over the imputed datasets using Rubins Rules [29]. All analyses were adjusted for ILAR category to determine the additional predictive power offered by the GRS. Analyses of change in COVs were adjusted for baseline values.

Results

Patient cohort

We considered 812 CYP with JIA with high-quality genotype data. Ninety-seven were excluded as they had non-European ancestry and two did not have a record of their ILAR category. This left 713 patients with genetic data and 1 year follow-up available (Table 1). Within the cohort, the median age of disease onset was 6.12 years and 65% were female. Oligoarticular JIA and RF negative polyarticular JIA were the most common JIA subtypes (Table 1).

Association of GRS with baseline measures

The GRS showed a normal distribution, with a mean score of 4.71 (s.d. 0.90) in our cohort (Fig. 1). Testing the high- and low-risk groups (quintile 5 and 1 of GRS, respectively) for association with COVs showed that CYP in the high-risk group have a lower age at onset and age at presentation by ~2.5 years (P<0.001) (median age at onset in low- and high-risk groups, respectively, 7.79 and 3.51) (median age at presentation in low- and high-risk groups, respectively, 9.06 and 4.05) (Table 2). The continuous GRS was associated with both age of onset and age at presentation.

![Histogram of JIA GRS](https://academic.oup.com/rheumatology)

**TABLE 1 Baseline characteristics**

| Variable | Value = n (%) or median (IQR) at baseline | Patients with available data at baseline n (%) | Patients with available data at 1-year n (%) |
|----------|------------------------------------------|-----------------------------------------------|---------------------------------------------|
| Age at onset (years) | 6.12 (2.65–10.36) | 703 (98.60) | — |
| Age at first presentation (years) | 6.89 (11.16–3.27) | 708 (99.30) | — |
| Gender | | 713 (100) | — |
| Female | 466 (65.36) | — | — |
| Active joint count | 2 (1–6) | 657 (92.15) | 638 (89.48) |
| Limited joint count | 1 (1–4) | 657 (92.15) | 638 (89.48) |
| Physician global assessment (10 cm VAS) | 3.1 (1.80–5.40) | 480 (67.32) | 472 (66.20) |
| Patient/parent global assessment (10 cm VAS) | 2.5 (0.60–5.10) | 535 (75.04) | 517 (72.51) |
| CHAQ (0–3) | 0.75 (0.25–1.43) | 543 (76.16) | 509 (71.39) |
| ESR (mm/h) | 21 (8–49) | 513 (71.95) | 299 (41.94) |
| ILAR | | 713 (100) | — |
| Systemic (%) | 49 (6.87) | — | — |
| Persistent oligoarthritis (%) | 305 (42.78) | — | — |
| Extended oligoarthritis (%) | 43 (6.03) | — | — |
| RF negative polyarthritis (%) | 171 (23.98) | — | — |
| RF positive polyarthritis (%) | 23 (3.23) | — | — |
| ERA (%) | 39 (5.45) | — | — |
| Psoriatic JIA (%) | 54 (7.57) | — | — |
| Undifferentiated (%) | 29 (4.07) | — | — |

CHAQ: childhood assessment questionnaire; ERA: enthesitis-related arthritis; ILAR: International League of Associations for Rheumatology classification criteria; VAS: visual analogue scale.
Table 3 shows the average change in each of the measured outcomes from baseline to 1 year. The median across all of the variables improved from baseline to 1 year follow-up. Prior to imputation there were high levels of missing data across all variables, with the highest for ESR as this is not routinely measured in UK paediatric rheumatology clinics unless a specific indication exists.

Multivariable linear regression showed that high or low GRS was not significantly associated with change in any of the outcome variables from BL to 1 year (Table 4).

Discussion

Recent developments in treatments including the development of biologics, increased use of combination therapy and the move towards a treat-to-target strategy [30] have improved JIA outcomes generally, making remission an achievable target and have increased the expectations of clinicians, parents and patients. Prolonged synovial inflammation, if not properly treated, can lead to irreversible changes in the structure of the joint. Increasing our understanding of disease outcome...
|                            | Median (IQR) quintile 1 | Median (IQR) quintile 5 | Coeff (adjusted BL) | 95% CI (adjusted BL) | P-value (adjusted BL) | Coeff (adjusted for BL and ILAR) | 95% CI (adjusted for BL and ILAR) | P-value (adjusted for BL and ILAR) |
|---------------------------|-------------------------|-------------------------|---------------------|---------------------|----------------------|----------------------------------|----------------------------------|----------------------------------|
| Change in active joint count | -1 (-4-0)               | -1.5 (-4-0)             | -0.39               | -1.23, 0.45         | 0.35                 | -0.38                           | -1.22, 0.46                      | 0.37                             |
| Change in limited joint count | -1 (-3-0)               | -1 (-3-0)               | -0.30               | -1.09, 0.48         | 0.45                 | -0.27                           | -1.06, 0.52                      | 0.50                             |
| Change in physician global assessment (10 cm VAS) | -2.35 (-4.35-0.55)      | -2.75 (-4.4-0.9)        | -0.42               | -0.93, 0.09         | 0.11                 | -0.42                           | -0.94, 0.09                      | 0.11                             |
| Change in parent global assessment (10 cm VAS) | -0.9 (-2.6-0.1)         | -1 (-3-0)               | -0.24               | -0.87, 0.39         | 0.45                 | -0.24                           | -0.87, 0.38                      | 0.44                             |
| Change in CHAQ             | -0.25 (-0.63-0)         | -0.13 (-0.63-0)         | 0.0005              | -0.18, 0.18         | 0.99                 | 0.0004                          | -0.18, 0.18                      | 0.99                             |
| Change in ESR (mm/h)       | -16 (-50-0.3)           | -15 (-33-0)             | 3.98                | -4.81, 12.77        | 0.36                 | 3.74                            | -5.11, 12.60                     | 0.40                             |

Association of high and low GRS groups with change in outcome from baseline to 1 year. The JIA GRS was split into quintiles: Q1 low risk, Q5 high risk. Association of the low and high risk groups was tested with change in each of the outcome variables after adjusting for BL measures, before and after adjusting for ILAR category. BL: baseline; Coeff: \( \beta \) coefficient; IQR: interquartile range.
will not significantly influence our results. If CYP were receiving treatment, it is unlikely that treatment would be directly associated with the GRS, as treatment does not differ due to genetics directly but by onset/severity, and therefore would not be a true confounder. The cohort represents a typical cohort of JIA patients treated according to current NHS guidelines in a rheumatology clinic; this means that any significant findings can be more easily applied to a real clinical setting.

The majority of genetic studies in JIA have been carried out in oligoarticular JIA and RF negative polyarticular JIA subtypes (referred to as polygos) as these are the most common categories of JIA and have been shown to be the most homogeneous in terms of genetics and clinical features. Conducting GWAS in other JIA subtypes has been more challenging due to the rarity of these categories. Here we have included all SNPs reaching genome-wide significance in the immunochip study that focussed on polygos [20], the most recent reaching genome-wide significance in the immunochip these categories. Here we have included all SNPs subtypes has been more challenging due to the rarity of these categories. Here we have included all SNPs reaching genome-wide significance in the immunochip study that focussed on polygos [20], the most recent GWAS of JIA that included all subtypes [22] and a GWAS that identified SNPs associated with systemic JIA into our GRS [21]. Where the same genomic region was identified in multiple studies, but different lead (most strongly associated) SNPs were reported, we used the lead SNP from the most recent GWAS as this included all subtypes, was imputed to the most recent reference panel and included the most homogeneous population (European ancestry CYP from the UK only). All SNPs in the GRS were weighted by the beta coefficient (log-odds ratio) of the SNP from the published GWAS [22].

As some SNPs in our GRS were identified in polygo JIA, this may have missed SNPs associated with other JIA categories. We have attempted to control for this by adjusting for ILAR subtype. In addition, a proportion of the samples in our study will overlap with the Immunochip study and all of our samples will have been included in the GWAS, both studies identified the majority of the susceptibility SNPs included in our GRS; however, although this overlap is significant, if anything it should have biased the results to be more positive. Overlap in JIA cohorts is often avoidable due to the rarity of the disease and the lack of studies with comprehensive outcome data. In addition, we are testing the association of the GRS with different outcomes and therefore, as we are not trying to predict JIA, the independence of the samples is less important. To investigate this further, we created independence between the cohorts by re-running the susceptibility GWAS analysis excluding this test cohort to re-define the weights and showed this had no impact on the beta coefficients (Supplementary Fig. S1, available at Rheumatology online). Also of note, each locus is represented by a single index SNP and further independent effects would not be captured by the current GRS. This is perhaps a limitation of the current analyses and is something to consider for future exploration.

Another potential consideration is the role of index bias or Berkson’s paradox [34], which occurs when multiple risk factors for a condition are also risk factors for the disease itself. Researchers may commonly find that well-established risk factors do not associate with/ have influence on disease risk. In such paradoxical cases, this is caused by limiting the patient cohort based on the disease itself and inducing correlation between the independent causes of disease. A popular example is known as the ‘obesity paradox’. Obesity has been found to be a strong predictor of cardiovascular disease (CVD) in multiple studies, even in the absence of other risk factors [35]. However, it has also been observed that after the onset of CVD, those with a higher BMI tend to survive longer [36]. One explanation is that CVD patients with high BMI may have lower levels of other risk factors for CVD. If having lower levels of the other risk factors increases survival, then high BMI may also be associated with increased survival rates.

In this study, the SNPs in the GRS are risk factors for JIA, as are the outcome variables. By restricting the study population to JIA patients, this induces dependence between the previously independent risk factors, even when they would not be associated in the general population, creating a spurious association between the two risk factors. If possible, future studies should consider adjusting for environmental factors (e.g. prior infection, maternal smoking, etc.) that may increase susceptibility to JIA, to aid in understanding whether these susceptibility SNPs do have an independent association with outcome. It is important to be aware of this potential confounding factor; however, studies of outcome cannot be performed in the general population. The ideal scenario would be to conduct a large-scale GWAS of outcome in JIA. However, no GWAS of outcome has ever been carried out, due to the challenge of collecting adequate numbers of cases with detailed clinical outcome data as well as DNA.

In conclusion, we have shown that known genetic susceptibility variants are poor predictors of changes in JIA core outcomes over time and we do not support the use of GRS of JIA susceptibility for the prediction of these outcomes. A GWAS of outcome is now required to identify true genetic predictors. It is hoped that efforts to standardize data collection and collaboration between research groups will make this a possibility.

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Data availability statement
Data available on request. The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary data
Supplementary data are available at Rheumatology online.

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