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SHORT COMMUNICATION

Association of the AFF3 gene and IL2/IL21 gene region with juvenile idiopathic arthritis

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Recent genetic studies have led to identification of numerous loci that are associated with susceptibility to autoimmune diseases. The strategy of using information from these studies has facilitated the identification of novel juvenile idiopathic arthritis (JIA) susceptibility loci, specifically, PTPN22 and IL2RA. Several novel autoimmune susceptibility loci have recently been identified, and we hypothesise that single-nucleotide polymorphisms (SNPs) within these genes may also be JIA susceptibility loci. Five SNPs within the genes AFF3, IL2/IL21, IL7R, CTLA4 and CD226, previously associated with multiple autoimmune diseases were genotyped, in a large data set of Caucasian JIA patients and controls, and tested for association with JIA. We identified two susceptibility loci for JIA, AFF3 and the IL2/IL21 region and additional weak evidence supporting an association with the CTLA4 and IL7R genes, which warrant further investigation. All results require validation in independent JIA data sets. Further characterisation of the specific causal variants will be required before functional studies can be performed.
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Keywords: *autoimmune; juvenile idiopathic arthritis; CTLA4; AFF3; IL2*

Introduction

Autoimmune diseases are caused by dysregulation of the immune system leading to an immune response to self-tissue. Autoimmune diseases are complex genetic diseases and in the last few years great progress has been made in the search for susceptibility loci.[1,2] As more confirmed autoimmune disease susceptibility loci are identified, an interesting story is emerging in that many of these loci predispose to more than one autoimmune disease. This confirms the hypothesis that shared alleles contribute to a spectrum of diseases and suggests that common immunological pathways are involved in susceptibility to these phenotypically distinct diseases.[3]

Juvenile idiopathic arthritis (JIA) is another complex genetic autoimmune disease characterised by chronic inflammatory disease in children. It is a group of heterogeneous disorders but encompasses all forms of arthritis of unknown aetiology that starts before the age of 16 and which persists for at least 6 weeks.[4] The strategy of using information from autoimmune disease genome-wide association studies or candidate gene studies have facilitated the search for novel JIA susceptibility loci. Indeed two recently identified confirmed JIA susceptibility loci, *PTPN22*[5] and *IL2RA*[6] are putative autoimmune susceptibility genes as they also show association with rheumatoid arthritis (RA),[5,7] type I diabetes (T1D)[7,8] and Graves' disease.[9,10] In addition, using a strategy of examining confirmed RA susceptibility loci in JIA, we have recently reported evidence for association of two further loci (*TRAF1/C5* and *STAT4*) with JIA susceptibility.[11]

Several novel putative autoimmune susceptibility loci have recently been identified with association with multiple autoimmune diseases. These include the IL2/21 region on chromosome 4q23[12,13] and the genes encoding *IL7R*,[14–16] *CTLA4*,[17] *AFF3*[14] and *CD226*.[18] We hypothesise that these genes may also confer susceptibility to JIA and, therefore, the aim of this study was to determine whether single-nucleotide polymorphisms (SNPs) within these genes are also associated with susceptibility to JIA.

Results and discussion

In this study, using a strategy of examining previously associated autoimmune loci in JIA, we have identified association of two loci with JIA susceptibility (Table 1). First, we show association of a SNP (rs1160542) in the 5′ region of the *AFF3* gene (Table 1), a gene that is preferentially expressed in lymphoid cells and has a potential regulatory role in lymphoid development.[19] This SNP has been associated with RA[20] and a perfect proxy SNP ($r^2 = 1$), rs9653442 has been associated with

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Table 1 Association analysis results for those SNPs associated with multiple autoimmune diseases in a cohort of patients with JIA

Marker	*Chr*	*Gene*[a]	*HWE controls*	*Major allele/minor allele (1/2)*	*MAF cases*	*MAF controls*	*Genotype frequency cases (%)*[b]			*Genotype frequency controls (%)*[c]			*Trend test P-value*[d]	*Allelic OR (95% CI)*
							22	*12*	*11*	*22*	*12*	*11*		
rs1160542	2	*AFF3*	0.32	A/G	0.5	0.45	217 (23.7)	483 (52.8)	215 (23.5)	574 (19.3)	1493 (50.3)	900 (30.3)	2.05×10^{-5}	1.25 (1.13–1.39)
rs3087243	2	*CTLA4*	0.74	G/A	0.43	0.46	180 (19.7)	428 (46.8)	306 (33.5)	634 (20.8)	1523 (50.0)	892 (29.3)	0.05	0.9 (0.81–1.0)
rs6822844	4	*IL2/IL21*	0.19	G/T	0.15	0.18	22 (2.3)	232 (24.8)	683 (72.9)	125 (3.6)	1003 (29.0)	2326 (67.3)	0.0006	0.78 (0.67–0.9)
rs6897932	5	*IL7R*	0.06	C/T	0.27	0.29	62 (6.6)	377 (40.0)	504 (53.4)	267 (7.6)	1482 (42.3)	1756 (50.1)	0.06	0.9 (0.8–1.01)
rs763361	18	*CD226*	0.84	C/T	0.48	0.46	222 (23.5)	464 (49.2)	257 (27.3)	745 (21.2)	1750 (49.9)	1012 (28.9)	0.13	1.08 (0.98–1.2)

Abbreviations: Chr, chromosome; HWE, *P*-value statistic for Hardy–Weinberg equilibrium test; JIA, juvenile idiopathic arthritis; MAF, minor allele frequency; SNP, single-nucleotide polymorphism. A Bonferroni correction of five was applied to correct for the number of loci studied, resulting in a *P*-value threshold of 0.01 for claims of significance. Genotyping was performed using the Sequenom iPLEX platform. A 90% sample quality control rate and 90% SNP genotyping success rate was imposed on the analysis.

[a]The gene name refers to the nearest gene in the region although SNPs are not necessarily intra-genic.

[b]UK Caucasian JIA patients ($n = 1054$) from three sources. The British Society for Paediatric and Adolescent Rheumatology (BSPAR) National Repository of JIA ($n = 654$), a cohort of UK Caucasian patients with long-standing JIA ($n = 201$), described previously[29] and a third cohort collected as part of the Childhood Arthritis prospective Study (CAPS), a prospective inception cohort study of JIA cases from five centres across United Kingdom ($n = 199$).[30]

[c]Healthy Caucasian control DNA samples were available from five centres in the United Kingdom as described previously[31]; Manchester, 924 controls (including 228 in 1958 birth cohort controls); Sheffield, 995 controls; Leeds 532 controls; Aberdeen 862 controls; Oxford 536 controls, total control sample size = 3531.

[d]Genotype and allele frequencies were compared between cases with JIA and controls using the Cochrane–Armitage trend test implemented in PLINK[32] and allelic odds ratios (ORs) and their 95% confidence intervals (CIs) calculated.

T1D[14] with similar odds ratio and allele frequencies to that observed in this study of JIA.

Second, we found strong association of a SNP (rs6822844) mapping within the *IL2–IL21* locus on chromosome 4q27, which has previously been associated with RA, T1D and coeliac disease (Table 1).[12,13] The SNP lies approximately 24 kb 5′ of the *IL21* gene. The SNP lies within a block of high linkage disequilibrium, which contains four genes, *KIAA1109*, *TENR*, *IL2* and *IL21*. As for the other diseases, it is the common allele, which predisposes to JIA. This association confirms a recently published association of the *IL2_IL2* region with JIA susceptibility.[21] We performed a meta-analysis of the two studies, which yielded highly significant evidence for association (odds ratio 0.77 95% confidence interval 0.69–0.87, $P = 1 \times 10^{-5}$) with no evidence for heterogeneity between the two cohorts ($P = 0.81$). This finding is interesting in light of the previous confirmed association of the *IL2RA* gene with JIA[6] and may suggest that the IL2 pathway is particularly important in JIA susceptibility.

We found a weak trend toward association of a SNP in the *IL7R* gene with JIA (Table 1), in line with the previous association of this SNP with RA, T1D[14] and multiple sclerosis[15,16] the common allele of the SNP was increased in cases compared with controls, although this did not achieve statistical significance. However, this study was under-powered with only 18% power to detect an effect (Supplementary Table 2). Therefore, additional independent studies and meta-analyses of this SNP will be required to confirm it as associated with JIA susceptibility. The SNP is a non-synonymous SNP within exon 6 of *IL7R* and has a functional effect on gene expression, resulting in altered ratios of soluble and membrane-bound isoforms of the protein.[15]

SNPs within the *CTLA4* gene, previously associated with T1D and autoimmune thyroid disease[17] have previously been examined in JIA with conflicting results.[22,23] This may reflect true genetic heterogeneity at this locus or may be due to the modest sample sizes used in previous investigations. We found a weak association of the *CTLA4 CT60* SNP (rs3087243) with UK JIA cases (Table 1), although this study only had 53% power to detect an effect (Supplementary Table 2). However, no evidence for association of this SNP with JIA was detected in a recent large study of US JIA families and controls.[23] We used the Cochran–Mantel–Haenszel test to perform a meta-analysis combining data from this study and the Prahalad study; this yielded weak but statistically significant evidence for association (odds ratio 0.92 95% confidence interval 0.84–1.0, $P = 0.05$) with no evidence for heterogeneity (by Breslow–Day test) between the two cohorts ($P = 0.44$). Further analysis of this SNP in independent data sets followed by meta-analysis will be essential to robustly determine whether *CTLA4* represents a JIA susceptibility locus. It is obviously a good candidate as an autoimmune susceptibility locus because of its role as a negative regulator of T-cell activation.[17] Furthermore, the CT60 SNP is found within the 3′ untranslated region, in which the G allele is associated with susceptibility to several autoimmune diseases and also has a functional effect of lower mRNA levels of the soluble CTLA4 isoform.[17]

Finally, a non-synonymous SNP, rs763361, in exon 7 of the *CD226* gene has recently been associated with multiple autoimmune diseases including T1D, multiple

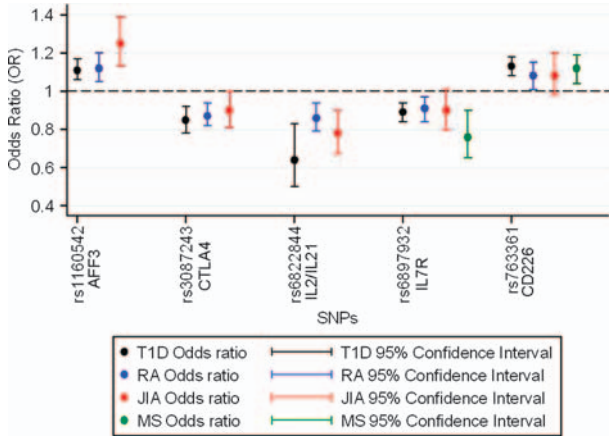

Figure 1 Plot of odds ratios for minor allele for SNPs previously associated with autoimmune disease, comparison with JIA. Plots of odds ratios and 95% confidence intervals for the association analysis of all SNPs, results in T1D (black dots and lines), in RA (blue dots and lines), in JIA (red dots and lines) and in MS (green dots and lines). References[12,14,16–18] and Barton (2009) submitted.

sclerosis and possibly autoimmune thyroid disease and RA.[18] In our total JIA analysis, we found no significant association of the SNP with JIA (Table 1). However, we only had 24% power to detect an effect (Supplementary Table 2).

Figure 1 shows a comparison between the association analysis results in T1D, RA, multiple sclerosis and JIA. For all the SNPs tested, the same allele was associated with JIA as was associated with the other autoimmune diseases and effect sizes are similar. Hence, the failure to confirm association with *CTLA4* and *IL7R* at the corrected threshold could be due to a lack of statistical power (53 and 18%, respectively) (Supplementary Table 2). It has not always been the case for the overlapping autoimmune disease susceptibility loci, that the same allele is associated. For example in *PTPN22*, the minor allele of the R620W SNP is associated with greater risk of developing RA, JIA, T1D and SLE but is protective for Crohn's disease.[24,25] There is also emerging data suggesting that one of the associated SNPs at the *IL2RA* locus confers differing risk and protective effects for T1D and multiple sclerosis.[26,27]

JIA is a phenotypically heterogeneous disease and can be classified into more clinically homogeneous diseases using the ILAR classification criteria (Supplementary Table 1).[28] However, comparing each of the ILAR subtypes separately against controls would result in a large number of hypothesis tests. Therefore, we first examined whether there was evidence of a difference in allele frequencies between the seven ILAR subtypes. Differences between subtypes were assessed using χ^2 tests on the 7×2 tables. Only when a difference was found ($P < 0.05$) were separate odds ratios and 95% confidence intervals calculated for the subgroups. In all cases, this was not significant ($P > 0.05$) (data not shown). Therefore, further stratification by ILAR subtype was not performed. Larger sample sizes will be required to fully examine subgroup differences.

In conclusion, adopting the strategy of targeting loci with previous evidence for association in multiple autoimmune diseases has identified two novel JIA loci, *AFF3* and the *IL2/IL21* locus.

Conflict of interest

The authors declare no conflict of interest.

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Appendix

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