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CHAPTER 4

CD226 (*DNAM-1*) IS ASSOCIATED WITH SUSCEPTIBILITY TO JUVENILE IDIOPATHIC ARTHRITIS

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ABSTRACT

Objectives

Juvenile idiopathic arthritis (JIA) is considered a complex genetic autoimmune disease. We investigated the association of genetic variants previously implicated in JIA, autoimmunity and/or immunoregulation, with susceptibility to JIA.

Methods

A genetic association study was performed in 639 JIA patients and 1613 healthy controls of North-West European descent. Ninety-three single nucleotide polymorphisms (SNPs) were genotyped in a candidate gene approach. Results of the entire JIA patient group (all subtypes) were compared to results obtained, alternatively, with a clinically homogeneous patient group including only oligoarticular and rheumatoid factor (RF) negative polyarticular JIA patients (n=493). Meta-analyses were performed for all SNPs that have been typed in other Caucasian JIA cohorts before.

Results

SNPs in or near *PTPN22*, *VTCN1*, the *IL2-IL21* region, *ANKRD55*, and *TNFA* were confirmed to be associated with JIA (p<0.05), strengthening the evidence for involvement of these genes in JIA. In the majority of these replicated SNPs, effect sizes were larger when analysing a homogeneous patient cohort than when analysing all subtypes. We identified two novel associations with oligoarticular and RF negative polyarticular JIA: *CD226* rs763361 (OR 1.30, 95%-CI 1.12-1.51, p=0.0006) and *CD28* rs1980422 (OR 1.29, 95%-CI 1.07-1.55, p=0.008). Meta-analyses including reported studies confirmed the association of both SNPs with susceptibility to JIA (OR 1.16, p=0.001 and OR 1.18, p=0.001, for rs763361 and rs1980422 respectively).

Conclusions

The *CD226* gene has been identified as novel association with JIA, and a SNP near *CD28* as a suggestive association. Both genes are probable candidate risk factors since they are involved in costimulation of T cells.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood. Prevalence numbers vary from 4 to 400 per 100,000 children.[1] JIA comprises a heterogeneous group of conditions that share chronic arthritis with onset before the age of sixteen. Seven distinct subtypes have been defined by the International League of Associations of Rheumatologists (ILAR) based on clinical characteristics and laboratory parameters.[2] However, phenotypic overlap between subtypes does exist, particularly between oligoarthritis (persistent and extended) and rheumatoid factor (RF) negative polyarthritis. These subtypes are only distinguished on the basis of the number of affected joints at onset and during the course of the disease.[3] A proportion of these patients have circulating antinuclear antibodies (ANA) and are specifically at risk for developing JIA-associated uveitis.[3]

The pathogenesis of JIA is not well understood. It is considered an autoimmune disease in which a deregulated T cell response towards an, as yet unidentified, self-antigen causes joint inflammation.[4] In most subtypes, synovial inflammation, which eventually leads to bone erosion, is associated with an overproduction of pro-inflammatory cytokines, such as TNF-α and IL-17.[5-9] JIA is a complex trait in which both genetic and environmental factors seem to be involved. Ethnic differences in epidemiologic studies,[1,10] as well as an increased risk of JIA for relatives of patients (sibling recurrence risk ratio λ_S of 12),[11-13] form evidence for genetic contribution to the risk of JIA.

It has become increasingly clear that autoimmune diseases cluster in individuals and families.[14,15] In line with this, genetic variations have been identified that are associated with more than one autoimmune disease, like rheumatoid arthritis (RA), type 1 diabetes mellitus, autoimmune thyroid disease, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis, and also JIA.[16-20] These results imply the existence of general genetic susceptibility to autoimmune diseases.

Identification of genetic risk variants could contribute to understanding of disease pathways, improve diagnosis of (subtypes of) JIA, and ultimately improve prognosis by providing new targets for therapy. Both candidate gene and genome-wide association studies (GWAS) have been performed to elucidate the genetic basis of JIA. Compared to more common autoimmune diseases, until recently JIA cohorts were small and heterogeneous. Only few genetic associations had been replicated, such as *PTPN22* and the major histocompatibility complex (MHC) region.[21,22] Other (suggestive) JIA susceptibility loci have been reported, but not confirmed, such as *ANKRD55* on 5q11.[22] Nevertheless, replication of these loci is essential to exclude false positive associations. Therefore we investigated in a Caucasian JIA cohort genetic loci previously implicated in JIA. Additionally, we investigated the association of genetic loci implicated in autoimmunity and/or immunoregulation with JIA. Analyses were performed in both a large but relatively heterogeneous JIA patient cohort (including all subtypes), and a smaller but phenotypically more homogeneous patient group (including only the persistent and extended oligoarticular and RF negative polyarticular subtypes).

METHODS

Subjects

DNA was available from 639 JIA patients with all subtypes, recruited through seven collaborating paediatric rheumatology referral centres in The Netherlands, Belgium, Germany, and Switzerland. All patients were of self-reported or parent-reported North-West European Caucasian descent. JIA cases were classified according to the revised ILAR criteria.[2] The patient group contained 263 patients with persistent oligoarthritis, 88 with extended oligoarthritis, and 142 with RF negative polyarthritis, resulting in a homogeneous group of 493 patients (Table 1).

DNA samples from healthy Caucasian controls were collected from three sources. See online supplementary methods for a detailed description of the control panels. Of the 93 markers that were successfully typed in the JIA patients, 40 were typed in 869 controls and 53 in 1319 controls (supplementary Tables S1, S2).

All patients and controls provided informed consent. The institutional review boards of all participating centres approved this study.

Genotyping

We genotyped single nucleotide polymorphisms (SNPs) adopting a candidate gene approach. The choice for specific genes and/or SNPs was based on previous reports suggesting involvement in JIA, other autoimmune diseases and/or immunoregulation. 93 SNPs located in 57 genes/loci passed quality control, listed in supplementary Table S2. See online supplementary methods for a detailed description of genotyping methods.

Statistical analysis

Allele frequencies were compared between JIA cases and controls. Allelic odds ratios (OR) and 95% confidence intervals (CI) were calculated using the allelic case-control association test in PLINK.[23] These ORs correspond to the genotypic ORs of an additive model. We differentiated between loci that have been associated with JIA before ('JIA replication loci'; 36 of 93 successfully typed SNPs) and loci that have not been impli-

Table 1
Patient characteristics of the JIA cohort

	n	(%)
Total cohort	639	
Gender		
Female	439	(69)
Male	200	(31)
Origin		
The Netherlands	324	(51)
Belgium	94	(15)
Germany	93	(15)
Switzerland	128	(20)
Subtype		
Persistent oligoarthritis	263	(41)
Extended oligoarthritis	88	(14)
RF negative polyarthritis	142	(22)
RF positive polyarthritis	22	(3)
Systemic JIA	73	(11)
Psoriatric arthritis	4	(<1)
Enthesitis related arthritis	3	(<1)
Undifferentiated JIA	44	(7)
ANA status		
Positive	280	(44)
Negative	229	(36)
Inconclusive/unknown	130	(20)
Family history [a]		
AID in 1st degree relative	69	(16)
AID in 1st or 2nd degree relative	169	(38)

RF: rheumatoid factor; ANA: antinuclear antibodies; AID: autoimmune disease
a) Family history known of 442 patients

cated in JIA before (57 SNPs) (supplementary Table S2). For analysis of 'replication loci' we included patients with all JIA subtypes, to conform to reported studies that revealed these JIA loci. Because there was a prior probability that these loci would be associated with JIA in our study too, a p value < 0.05 was considered significant for these SNPs. We also performed the association analyses including only the most homogeneous JIA subtypes (persistent and extended oligoarthritis and RF negative polyarthritis, n=493). For the other 57 SNPs we analysed these 493 homogeneous JIA patients by comparing them as a group to controls. To adjust for multiple testing, a Bonferroni correction should be applied to the results for these 57 SNPs, leading to a significance threshold

of $p < 0.001$. Additionally, we performed ILAR subtype-specific case-control analyses (within the homogeneous patient group) for all 93 SNPs, and also compared all ANA positive patients within this group to controls (supplementary Table S3).
Meta-analyses were performed for all SNPs that have been investigated in JIA before (supplementary Tables S4, S5). We included reported genetic association studies in Caucasian case-control cohorts (including a mixed set of JIA subtypes), in which the same SNPs have been typed. We excluded studies for which data necessary to calculate allelic ORs were not available. Not all JIA replication loci were included for meta-analyses because of these inclusion and exclusion criteria. In case of overlapping individuals in reported studies, we only included the study with the largest JIA cohort. For meta-analyses of rs1980422 near *CD28* and rs763361 in *CD226*, we performed analyses in homogeneous (oligoarticular and RF negative polyarticular) JIA patients.[18,24,25] Because of the small number of studies included in the meta-analyses, a fixed-effects model was used in a Mantel-Haenszel test.
All statistical analyses were performed with use of the software PLINK v1.07 (http://pngu.mgh.harvard.edu/purcell/plink/).[23]

RESULTS

Replication of JIA loci

Thirty-six SNPs that have been previously reported to be associated with JIA were investigated in our entire JIA cohort consisting of 639 patients with all seven different subtypes. To conform to reported studies, all ILAR subtypes were included. Nine of 36 reported SNPs were confirmed to be associated ($p < 0.05$): *VTCN1* rs10923217, *KIAA1109* rs4505848, *IL21* rs1398553, *ANKRD55* rs6859219, *TNFA* rs1799724, rs1800750, rs361525, and rs1800610, and *MIF* rs755622 (Table 2). Because we propose to perform association studies only in a patient cohort as homogeneous as possible, additional analyses were limited to only oligoarthritis and RF negative polyarthritis (n=493). Although limiting the patient group led to fewer cases, all associations were still significant (Table 2). By performing analyses in the smaller, more homogeneous JIA cohort, the reported JIA SNPs *PTPN22* rs2476601 and *TNFA* rs1800629 were additionally confirmed. In the majority of these replicated associations, analysis in the more homogeneous patient cohort led to larger effect sizes. For all SNPs that had been investigated in Caucasian JIA cohorts before, a meta-analysis was performed. For 23 of 36 replication loci, appropriate data for meta-analyses were available, of which *PTPN22* rs2476601, *VTCN1* rs10923217, rs6669320, rs10923223 and rs12046117, *PTPRC* rs10919563, *AFF3* rs1160542, *CCR5* rs333, *TNFA* rs1799724,

Table 2. Association analyses of reported JIA loci

Chr	Position[a]	Gene/ region	SNP	Minor allele	MAF controls	MAF cases	*All JIA subtypes* OR (95% CI)	*All JIA subtypes* P (allelic)	*Only homogeneous JIA subtypesb* MAF cases	*Only homogeneous JIA subtypesb* OR (95% CI)	*Only homogeneous JIA subtypesb* P (allelic)	Reference
1	114377568	***PTPN22***	**rs2476601**	A	0.10	0.12	1.26 (1.00-1.59)	0.051	0.13	**1.32 (1.03-1.69)**	**0.02702**	54
1	117685992	*VTCN1*	rs6673837	A	0.20	0.21	1.04 (0.86-1.24)	0.7101	0.20	0.99 (0.82-1.21)	0.9474	55
1	117690758	*VTCN1*	rs2358817	T	0.08	0.07	0.83 (0.63-1.10)	0.1933	0.07	0.88 (0.65-1.19)	0.4164	55
1	117711911	*VTCN1*	rs2358820	A	0.07	0.06	0.89 (0.66-1.20)	0.4467	0.07	0.92 (0.67-1.26)	0.602	55
1	117730048	***VTCN1***	**rs10923217**	C	0.48	0.52	**1.20 (1.04-1.40)**	**0.01358**	0.52	**1.21 (1.03-1.42)**	**0.02079**	55
1	117730623	*VTCN1*	rs6669320	A	0.15	0.13	0.89 (0.72-1.11)	0.3032	0.13	0.89 (0.70-1.12)	0.3117	55
1	117746573	*VTCN1*	rs10923223	C	0.15	0.16	1.16 (0.95-1.42)	0.1571	0.16	1.09 (0.88-1.36)	0.4383	55
1	117751365	*VTCN1*	rs12046117	T	0.13	0.14	1.11 (0.89-1.37)	0.3522	0.13	1.04 (0.82-1.32)	0.7252	55
1	198700442	*PTPRC*	rs10919563	A	0.13	0.12	0.91 (0.74-1.13)	0.3853	0.11	0.86 (0.68-1.08)	0.195	20
2	100832155	*AFF3*	rs1160542	G	0.45	0.46	1.05 (0.92-1.21)	0.4699	0.46	1.05 (0.90-1.22)	0.5177	18
2	100835734	*AFF3*	rs10865035	A	0.46	0.47	1.05 (0.91-1.23)	0.4924	0.47	1.05 (0.89-1.24)	0.5762	LD[18]
2	113590390	*IL1B*	rs1143634	A	0.25	0.24	0.93 (0.79-1.11)	0.4424	0.24	0.95 (0.79-1.14)	0.5542	56
2	204732714	*CTLA4*	rs231775	G	0.37	0.35	0.91 (0.78-1.06)	0.2112	0.35	0.92 (0.78-1.09)	0.3251	LD[29]
3	46414947	*CCR5*	rs333	del	0.10	0.09	0.83 (0.65-1.05)	0.1155	0.08	0.81 (0.62-1.06)	0.1168	57
4	123132492	***KIAA1109***	**rs4505848**	G	0.36	0.40	**1.23 (1.07-1.42)**	**0.004019**	0.40	**1.20 (1.03-1.41)**	**0.01901**	58
4	123348345	*ADAD1*	rs11732095	G	0.08	0.07	0.90 (0.68-1.17)	0.4229	0.07	0.91 (0.68-1.23)	0.5508	LD[58]
4	123514528	*IL2-IL21*	rs4492018	A	0.24	0.21	0.85 (0.72-1.00)	0.05315	0.21	0.88 (0.73-1.05)	0.1495	LD[58]
4	123548068	***IL21***	**rs1398553**	T	0.33	0.38	**1.24 (1.07-1.43)**	**0.003359**	0.38	**1.22 (1.05-1.43)**	**0.0109**	LD[58]
5	55438580	***ANKRD55***	**rs6859219**	A	0.22	0.18	**0.77 (0.64-0.92)**	**0.003175**	0.17	**0.74 (0.61-0.90)**	**0.002953**	LD[22]
6	31542482	***TNFA***	**rs1799724**	T	0.10	0.13	**1.37 (1.09-1.73)**	**0.007318**	0.13	**1.40 (1.09-1.79)**	**0.007489**	LD[59]
6	31542963	***TNFA***	**rs1800750**	A	0.02	0.01	**0.37 (0.17-0.80)**	**0.008935**	0.01	**0.36 (0.15-0.86)**	**0.01635**	LD[59]
6	31543031	***TNFA***	**rs1800629**	A	0.17	0.15	0.87 (0.71-1.06)	0.172	0.14	**0.79 (0.63-0.99)**	**0.04234**	60

Table 2. Association analyses of reported JIA loci (continued)

							All JIA subtypes		*Only homogeneous JIA subtypesb*			
Chr	**Position[a]**	**Gene/ region**	**SNP**	**Minor allele**	**MAF controls**	**MAF cases**	**OR (95% CI)**	**P (allelic)**	**MAF cases**	**OR (95% CI)**	**P (allelic)**	**Reference**
6	31543101	*TNFA*	rs361525	A	0.05	0.03	**0.56 (0.37-0.83)**	**0.003987**	0.03	**0.55 (0.35-0.86)**	**0.007526**	59
6	31543827	***TNFA***	**rs1800610**	A	0.10	0.13	**1.34 (1.06-1.69)**	**0.01332**	0.13	**1.38 (1.08-1.77)**	**0.009952**	LD[59]
6	31544189	*TNFA*	rs3093662	G	0.06	0.04	0.75 (0.53-1.05)	0.09238	0.04	0.75 (0.52-1.09)	0.1328	LD[59]
6	138006504	*TNFAIP3*	rs6920220	A	0.21	0.20	0.98 (0.82-1.18)	0.8275	0.20	0.98 (0.80-1.19)	0.821	16
7	128594183	*TNPO3*	rs10488631	C	0.10	0.10	1.00 (0.79-1.26)	0.9903	0.10	1.03 (0.80-1.33)	0.8078	20
10	6053163	*IL2RA*	rs12722605	T	0.14	0.15	1.03 (0.85-1.25)	0.7694	0.15	1.05 (0.85-1.30)	0.6622	LD[22]
10	6099045	*IL2RA*	rs2104286	G	0.25	0.25	0.97 (0.82-1.15)	0.7435	0.23	0.91 (0.76-1.10)	0.3382	61
10	6114660	*IL2RA*	rs41295061	A	0.09	0.09	1.02 (0.81-1.30)	0.8551	0.09	1.02 (0.79-1.32)	0.8834	61
16	11179873	*CLEC16A*	rs12708716	G	0.35	0.34	0.94 (0.82-1.09)	0.4245	0.33	0.92 (0.78-1.07)	0.2729	LD[62]
16	11249329	*CLEC16A*	rs6498169	G	0.34	0.36	1.08 (0.93-1.24)	0.3049	0.37	1.09 (0.93-1.28)	0.2653	62
22	24236392	***MIF***	**rs755622**	C	0.21	0.16	**0.69 (0.57-0.84)**	**0.0002126**	0.15	**0.67 (0.54-0.83)**	**0.0002084**	28
22	37544245	*IL2RB*	rs3218258	T	0.28	0.28	0.99 (0.85-1.15)	0.8765	0.27	0.97 (0.82-1.15)	0.7135	LD[22]
22	37544810	*IL2RB*	rs3218253	T	0.28	0.28	1.01 (0.87-1.18)	0.8677	0.28	0.99 (0.84-1.17)	0.9164	LD[22]
22	37551607	*IL2RB*	rs743777	G	0.34	0.33	0.97 (0.84-1.12)	0.6348	0.33	0.95 (0.81-1.12)	0.5386	LD[22]

Chr: chromosome; MAF: minor allele frequency; OR: odds ratio; CI: confidence interval; LD: in linkage disequilibrium with reported JIA locus
a) Base-pair position is based on NCBI dbSNP build 136
b) Patient group limited to oligoarticular (persistent and extended) and RF negative polyarticular JIA patients

TNFAIP3 rs6920220, *TNPO3* rs10488631, *IL2RA* rs2104286, and *CLEC16A* rs6498169 were significant (supplementary Table S4).

Novel JIA loci

An additional 57 SNPs, not reported to be associated with JIA before, located in or near autoimmune loci, were investigated in the homogeneous patient cohort. One SNP was strongly associated with JIA, *CD226* rs763361 (OR 1.30, 95% CI 1.12-1.51, p=0.0006). This SNP has not been reported to be associated with JIA before and represents a novel association (Table 3). The effect is particularly prominent in the persistent oligoarthritis patients (OR 1.39, p=0.0008) (supplementary Table S3). *CD226* rs763361 has been investigated before in two other Caucasian JIA cohorts and a non-significant trend of this SNP towards association with JIA (all subtypes) was reported (p=0.13[18]; p=0.059[25]). We performed a meta-analysis combining the results from our study and the published data. To limit clinical heterogeneity between study cohorts, only patients with oligo-articular and RF negative polyarticular JIA were included in this meta-analysis. The meta-analysis revealed a combined association of this *CD226* variant with JIA, OR 1.16, p=0.001 (supplementary Table S5, Figure S1).

Rs1980422 near *CD28* was revealed as a suggestive association (OR 1.29, 95% CI 1.07-1.55, p=0.008) which was not significant after correction for multiple testing (Table 3). The effect of this SNP is particularly prominent in ANA-positive patients (OR 1.52, p=0.0004) (supplementary Table S3). This SNP was investigated before in a GWAS in Caucasian (oligoarticular and RF-negative polyarticular) JIA patients and a trend towards association was reported (p=0.04).[24] Also for this SNP we performed a meta-analysis combining the results of the present and the reported study, which resulted in a combined association of rs1980422 with JIA, OR 1.18, p=0.001 (supplementary Table S5, Figure S1).

Table 3
Polymorphisms in immune related genes associated with homogeneous subtypes of JIA[a]

Chr	Position[b]	Gene/ region	SNP	Minor allele	MAF controls	MAF cases	OR (95% CI)	P (allelic)
2	204610396	*CD28*	rs1980422	C	0.22	0.27	1.29 (1.07-1.55)	0.008079
18	67531642	*CD226*	rs763361	T	0.47	0.54	1.30 (1.12-1.51)	0.0006295

Chr: chromosome; MAF: minor allele frequency; OR: odds ratio; CI: confidence interval
[a] Homogeneous subtypes include oligoarticular (persistent and extended) and RF negative polyarticular JIA patients. Only SNPs that are (suggestively) associated with p<0.05 are listed.
[b] Base-pair position is based on NCBI dbSNP build 136

Pooling our results with published non-significant associations (24 of 57 SNPs) revealed a potential novel association of *PRKCQ* rs4750316 with JIA (OR 0.90, p=0.01) (supplementary Table S5).

DISCUSSION

We investigated the role of 93 genetic markers previously associated with JIA or involved in autoimmunity or immunoregulation in a large Caucasian JIA cohort. We identified the *CD226* gene as a novel association with JIA, and a SNP near *CD28* as a suggestive association.

While this study was powered (>=80%) to detect associations with an effect size (OR) >= 1.4, for SNPs with a minor allele frequency >= 0.10 at an alpha of 0.05, replication is the golden standard in genetic association studies and essential to exclude false-positive results. Collecting a large, homogeneous patient cohort which generates sufficient power is challenging in JIA, given the relatively low prevalence. A recent large study in JIA with dense genotyping of immune-related disease loci, which was published whilst this study was in progress, has also shown that increasing sample size improves power to detect true JIA loci.[22] Although meta-analyses have limitations in case of publication bias and clinical heterogeneity between cohorts, they are also valuable for evaluating potentially false-positive or false-negative associations. Pooling of our and published results provides additional evidence for associations of 13 SNPs in 9 loci previously implicated in JIA. Furthermore, pooling of non-significant results from several studies suggests association of rs4750316 near *PRKCQ* with JIA, which is also an RA-locus.[26,27] However, heterogeneity within a cohort (e.g. by including clinically different JIA subtypes) can be a pitfall leading to false-negative results.

We compared results obtained by analysing the entire JIA patient group in a case-control study to, alternatively, only JIA patients with the two clinically most similar ILAR subtypes (persistent and extended) oligoarthritis and RF negative polyarthritis). Although limiting the inclusion to two JIA subtypes resulted in smaller patient numbers, the study had enough power to confirm well-established JIA loci, e.g. *PTPN22* and *TNFA*. In the majority of replicated SNPs, effect sizes were larger when analysing only the homogeneous cohort. This argues in favour of restricting analyses to a homogeneous patient cohort, as has also been performed in two recent large studies in JIA.[22,24]

The associated loci *PTPN22* (rs2476601), *VTCN1* (rs10923217), *KIAA1109* (rs4505848), *IL21* (rs1398553), *ANKRD55* (rs6859219), and *TNFA* (rs1799724, rs1800750, rs1800629, rs361525, rs1800610) were replicated in this study strengthening their involvement in JIA. Four of these were confirmed in a meta-analysis: *PTPN22* rs2476601, *VTCN1* rs10923217, and *TNFA* rs1799724 and rs361525. An additional nine JIA replication SNPs, not confirmed by this study, were significantly associated in the meta-analysis. All of these genes are also associated with RA and/or other autoimmune diseases and are probably involved in the regulation of the immune response. All genes except *ANKRD55* have obvious roles in immune processes. It should be noted that the C allele of rs755622 in the promoter region of *MIF* (encoding the proinflammatory cytokine macrophage migration inhibitory factor) is associated with protection to JIA in our study, but this conflicts with results from other JIA cohorts that suggest association of the C allele with susceptibility.[28-31] The reason for these opposing results is not clear, but the minor allele frequency (MAF) of this SNP in our control cohort is comparable to the MAF in other North-West European control cohorts.[29,32-34] Genetic studies of *MIF* in RA and inflammatory bowel disease have yielded similarly opposing results,[29,35-40] indicating that the role of this SNP in JIA and other autoimmune diseases is still unclear. The other investigated JIA loci, of which *IL2RA* and *IL2RB* reached genome-wide significance in a previous report, were not confirmed in our cohort, which might be due to insufficient power to detect modest risk loci.[22] A SNP in *IL2RA* was significant in the meta-analysis, underlining the importance of combining data from different JIA cohorts.

One of the strongest replicated associations with JIA is rs6859219, located at locus 5q11, in *ANKRD55*, an ankyrin repeat domain-containing gene with unknown function. This region has been recently identified by dense genotyping of immune-related disease loci in JIA patients.[22] Although nearby genes *IL6ST* and *IL31RA* encode proteins involved in immunity, SNPs in these genes are not in linkage disequilibrium with the associated SNP in *ANKRD55*. Ankyrin repeat domains are common protein structures and mediate protein-protein interactions. Although the precise function of *ANKRD55* is not known, it is specifically expressed in resting CD4+ T cells (http://www.amazonia.transcriptome.eu), which is interesting when a role in autoimmunity is presumed. Rs6859219 was previously found to be associated with RA in a GWAS and with multiple sclerosis.[41-43]

In addition to the confirmation of previously identified associations, two novel susceptibility loci for the most common JIA subtypes were discovered. *CD28* rs1980422 is only weakly associated, but is interesting because of its location between two immune related genes: *CD28* (approximately 10 kb away) and *CTLA4* or cytotoxic T-lymphocyte antigen-4 (approximately 129 kb away), a gene that is associated with multiple autoimmune diseases including RA, with conflicting results in JIA.[18,21,29,44,45] There is minimal linkage disequilibrium between rs1980422 and several SNPs in *CTLA4*. We also investigated the well-established general autoimmunity SNP rs231775 in *CTLA4*, but this SNP was not associated with JIA in this study. Both gene products have opposing roles in T cell activation. CD28 is expressed on the T cell surface and involved in costimulation of T cells. CTLA4 is expressed by T cells upon activation by antigen presenting cells. It functions as an attenuator of T cell activation by competing with CD28 for shared ligands (CD80 and CD86). Rs1980422 near *CD28* was associated with RA in a GWAS.[46] In a recent GWAS in JIA, this SNP was tested, but not significantly associated with JIA after correction for multiple testing.[24] Combining these results with ours in a meta-analysis resulted in a significant association. The *CD28* region has not been identified as a significant JIA susceptibility locus in a recent, large association study in which the ImmunoChip was used, but interestingly, this ImmunoChip study as well as the JIA GWAS revealed a strong association of SNPs in the region of *CD80*, coding for a ligand of CD28, with JIA.[22,24] The implication of three components of this costimulatory pathway, CD80, CTLA4 and CD28, in JIA and other autoimmune diseases is supportive for a role in autoimmune pathogenesis.

The most strongly associated novel SNP rs763361 is located in *CD226*, which encodes CD226 or DNAX accessory molecule 1 (DNAM-1). DNAM-1 is a type 1 membrane protein belonging to the Ig-supergene family. It is mainly expressed on T and NK cells and is involved in the adhesion and costimulation of these cells via its ligands CD112 and CD155.[47,48] The *CD226* region has not been identified as a (genome-wide significant) JIA susceptibility locus in the large association study with use of the ImmunoChip, which also captures *CD226*.[22] Nevertheless, a meta-analysis of our study with two previous candidate gene studies confirmed the association with JIA.[18,25] Furthermore, recent genetic studies have reported an association of this non-synonymous SNP (Gly307Ser) with susceptibility to multiple autoimmune diseases, as type 1 diabetes mellitus, autoimmune thyroid disease, multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus, denoting it as a general autoimmunity locus.[49,50] A fine-mapping study of the 18q22 region, in which the SNP lies, was performed in type 1 diabetes mellitus and multiple sclerosis patients by exonic resequencing and tag SNP mapping.[49] This study pointed out the SNP as a probable causal variant. However, this study cannot exclude other (rare) variants in linkage disequilibrium with rs763361 being the true causal variant. If rs763361 would be correlated with altered expression and/or signaling, this could explain the contribution of this variant to autoimmunity. DNAM-1 deficient mice show impaired control of viral infections and less cytotoxic activity against tumors compared to wild type mice, suggesting a form of immunodeficiency when CD226 function is impaired.[51,52] In another report in which the role of CD226 in experimental autoimmune encephalomyelitis (EAE, a model for multiple sclerosis) was studied, application of a monoclonal antibody against CD226 led to delayed onset and reduced severity of EAE.[53] This is suggestive for a role of CD226 in the development of autoimmune disease. By contrast, it is apparently contradictory that individuals that were homozygous for a *CD226* haplotype associated with susceptibility to systemic lupus erythematosus expressed lower *CD226* transcript levels and lower surface proteins on T cells and NK cells.[50] Replication in independent, homogeneous cohorts and additional fine-mapping and functional studies are needed to clarify the pathogenic implications of variation in these loci.

In summary, our data generate renewed interest for a role in JIA of two biological pathways that aid priming of T cells: the costimulatory mechanism involving CD28, CTLA4 and CD80/CD86, and the *CD226* gene, encoding the accessory molecule DNAM-1, which is a novel JIA susceptibility locus. This does not only contribute to knowledge of JIA pathogenesis, but targeting these T cell stimulating processes might also be of therapeutic interest.

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SUPPLEMENTARY DATA

Supplementary methods

Control subjects

1130 controls were healthy blood bank donors (758 randomly selected by the Immunogenetics and Transplantation Immunology (ITI) section of the Department of Immunohematology and Bloodtransfusion, and 372 by the Laboratory for Diagnostic Genome Analyses (LDGA) at Leiden University Medical Center, all from the region of Leiden, The Netherlands), 372 controls were anonymized individuals that requested genetic counselling at the LDGA regarding a monogenic disease in their families, but tested negative for this single genetic defect, and 111 controls were recruited via participating patients and their families (but unrelated) (supplementary Table S1). Due to limited availability of DNA, genetic markers were genotyped in different control cohorts. Of the 93 markers that were successfully typed in the JIA patients, 40 were typed in 869 controls and 53 in 1319 controls (supplementary Tables S1, S2).

DNA and genotyping

DNA was isolated from buccal swabs or a blood sample. We performed genotyping of 112 SNPs in 65 genes/loci by iPLEX MassARRAY according to the manufacturer's recommendations (Sequenom, San Diego, California, USA). Only SNPs exceeding a 90% call rate and no evidence for deviation from Hardy-Weinberg equilibrium in the control population ($p > 0.005$) were used for further analysis. 93 of 112 SNPs (83%) located in 57 genes/loci passed quality control, listed in supplementary Table S2. SNP call rates per individual exceeded 90%.

Supplementary Table S1
Control subjects

Set	Source	n	Type of control subjects
1	ITI	464	Healthy blood donors
2	ITI	294	Healthy blood donors
3	LDGA	372	Healthy blood donors
4	LDGA	372	Healthy relatives of monogenic disease patients
5	JIA families	111	Healthy unrelated acquaintances of JIA patients

ITI: Immunogenetics and Transplantation Immunology section; LDGA: Laboratory for Diagnostic Genome Analyses

Supplementary Table S2 Allele and genotype frequencies in oligoarticular (persistent and extended) and RF negative polyarticular JIA patients versus controls

Chr	Position[a]	Gene/ region	SNP	Minor allele	MAF controls	MAF cases	OR (95% CI)	P (allelic)	Genotype counts controls	Genotype counts cases	Typed in control sets[c]	Reported JIA locus[d]
									11 / 12 / 22[b]	11 / 12 / 22[b]		
1	2553624	*TNFRSF14-MMEL1*	rs3890745	G	0.32	0.30	0.90 (0.77-1.06)	0.2137	126 / 568 / 570	47 / 187 / 231	1, 3, 4, 5 (n = 1319)	no
1	12091210	*TNFRSF8-MIIP*	rs946461	T	0.26	0.29	1.15 (0.98-1.36)	0.09358	84 / 480 / 668	41 / 196 / 240	1, 3, 4, 5 (n = 1319)	no
1	12252955	*TNFRSF1B*	rs1061622	G	0.23	0.24	1.03 (0.85-1.24)	0.7678	44 / 309 / 492	34 / 160 / 281	1, 2, 5 (n = 869)	no
1	32729702	*LCK*	rs1004420	T	0.17	0.17	0.98 (0.80-1.19)	0.8087	46 / 332 / 839	11 / 135 / 314	1, 3, 4, 5 (n = 1319)	no
1	32743866	*LCK*	rs695161	C	0.48	0.47	0.97 (0.83-1.13)	0.6721	295 / 592 / 345	108 / 233 / 135	1, 3, 4, 5 (n = 1319)	no
1	114377568	*PTPN22*	rs2476601	A	0.10	0.13	1.32 (1.03-1.69)	0.02702	10 / 150 / 689	9 / 104 / 363	1, 2, 5 (n = 869)	yes
1	117685992	*VTCN1*	rs6673837	A	0.20	0.20	0.99 (0.82-1.21)	0.9474	40 / 265 / 544	19 / 154 / 302	1, 2, 5 (n = 869)	yes
1	117690758	*VTCN1*	rs2358817	T	0.08	0.07	0.88 (0.65-1.19)	0.4164	6 / 125 / 699	0 / 69 / 400	1, 2, 5 (n = 869)	yes
1	117711911	*VTCN1*	rs2358820	A	0.07	0.07	0.92 (0.67-1.26)	0.602	4 / 112 / 731	1 / 59 / 406	1, 2, 5 (n = 869)	yes
1	117730048	*VTCN1*	rs10923217	C	0.48	0.52	1.21 (1.03-1.42)	0.02079	201 / 397 / 239	132 / 232 / 109	1, 2, 5 (n = 869)	yes
1	117730623	*VTCN1*	rs6669320	A	0.15	0.13	0.89 (0.70-1.12)	0.3117	27 / 194 / 625	12 / 94 / 341	1, 2, 5 (n = 869)	yes
1	117746573	*VTCN1*	rs10923223	C	0.15	0.16	1.09 (0.88-1.36)	0.4383	13 / 221 / 614	15 / 119 / 341	1, 2, 5 (n = 869)	yes
1	117751365	*VTCN1*	rs12046117	T	0.13	0.13	1.04 (0.82-1.32)	0.7252	11 / 197 / 638	10 / 107 / 356	1, 2, 5 (n = 869)	yes
1	198700442	*PTPRC*	rs10919563	A	0.13	0.11	0.86 (0.68-1.08)	0.195	23 / 268 / 935	5 / 95 / 370	1, 3, 4, 5 (n = 1319)	yes
1	206946897	*IL10*	rs1800896	C	0.50	0.47	0.90 (0.77-1.06)	0.2119	219 / 408 / 219	92 / 238 / 115	1, 2, 5 (n = 869)	no
1	207015957	*IL19*	rs2243191	T	0.20	0.23	1.17 (0.96-1.43)	0.1209	27 / 283 / 536	21 / 155 / 261	1, 2, 5 (n = 869)	no
1	207038686	*IL20*	rs1400986	T	0.16	0.14	0.86 (0.69-1.08)	0.1975	23 / 230 / 595	7 / 122 / 344	1, 2, 5 (n = 869)	no
2	100832155	*AFF3*	rs1160542	G	0.45	0.46	1.05 (0.90-1.22)	0.5177	255 / 629 / 384	95 / 241 / 131	1, 3, 4, 5 (n = 1319)	yes
2	100835734	*AFF3*	rs10865035	A	0.46	0.47	1.05 (0.89-1.24)	0.5762	269 / 631 / 367	88 / 174 / 108	1, 3, 4, 5 (n = 1319)	yes
2	103070568	*IL18RAP*	rs917997	T	0.22	0.24	1.14 (0.94-1.37)	0.1782	45 / 283 / 519	29 / 172 / 272	1, 2, 5 (n = 869)	no
2	113537223	*IL1A*	rs17561	A	0.30	0.29	0.92 (0.77-1.09)	0.3289	74 / 366 / 406	32 / 194 / 226	1, 2, 5 (n = 869)	no
2	113542960	*IL1A*	rs1800587	A	0.31	0.28	0.89 (0.74-1.07)	0.2285	74 / 369 / 404	29 / 169 / 205	1, 2, 5 (n = 869)	no
2	113590390	*IL1B*	rs1143634	A	0.25	0.24	0.95 (0.79-1.14)	0.5542	57 / 306 / 485	20 / 185 / 269	1, 2, 5 (n = 869)	yes
2	113594867	*IL1B*	rs16944	A	0.33	0.35	1.11 (0.94-1.31)	0.2315	79 / 395 / 370	61 / 211 / 203	1, 2, 5 (n = 869)	no

Supplementary Table S2 Allele and genotype frequencies in oligoarticular (persistent and extended) and RF negative polyarticular JIA patients versus controls

Chr	Position[a]	Gene/ region	SNP	Minor allele	MAF controls	MAF cases	OR (95% CI)	P (allelic)	Genotype counts controls	Genotype counts cases	Typed in control sets[c]	Reported JIA locus[d]
2	162856148	*DPP4*	rs2268894	C	0.45	0.47	1.07 (0.91-1.25)	0.4192	164 / 437 / 247	99 / 246 / 130	1, 2, 5 (n = 869)	no
2	191835596	*STAT1*	rs3771300	C	0.48	0.50	1.10 (0.94-1.27)	0.2321	281 / 608 / 337	118 / 238 / 118	1, 3, 4, 5 (n = 1319)	no
2	191843445	*STAT1*	rs13010343	A	0.14	0.13	0.96 (0.77-1.20)	0.7449	29 / 287 / 924	10 / 107 / 354	1, 3, 4, 5 (n = 1319)	no
2	191845725	*STAT1*	rs1547550	C	0.35	0.34	0.95 (0.82-1.12)	0.5685	158 / 536 / 519	62 / 197 / 212	1, 3, 4, 5 (n = 1319)	no
2	191855521	*STAT1*	rs7562024	T	0.40	0.39	0.95 (0.82-1.11)	0.5502	203 / 579 / 447	71 / 221 / 174	1, 3, 4, 5 (n = 1319)	no
2	204610396	*CD28*	rs1980422	C	0.22	0.27	1.29 (1.07-1.55)	0.008079	65 / 433 / 759	30 / 144 / 203	1, 3, 4, 5 (n = 1319)	no
2	204732714	*CTLA4*	rs231775	G	0.37	0.35	0.92 (0.78-1.09)	0.3251	126 / 375 / 347	44 / 240 / 184	1, 2, 5 (n = 869)	yes
3	46414947	*CCR5*	rs333	del	0.10	0.08	0.81 (0.62-1.06)	0.1168	17 / 224 / 1028	5 / 68 / 392	1, 3, 4, 5 (n = 1319)	yes
3	58556841	*FAM107A*	rs13315591	C	0.07	0.08	1.13 (0.86-1.50)	0.3795	5 / 170 / 1092	2 / 71 / 397	1, 3, 4, 5 (n = 1319)	no
4	26108197	4p15	rs874040	G	0.31	0.29	0.93 (0.79-1.09)	0.3556	112 / 534 / 594	43 / 189 / 243	1, 3, 4, 5 (n = 1319)	no
4	123132492	*KIAA1109*	rs4505848	G	0.36	0.40	1.20 (1.03-1.41)	0.01901	170 / 567 / 538	73 / 222 / 166	1, 3, 4, 5 (n = 1319)	yes
4	123348345	*ADAD1*	rs11732095	G	0.08	0.07	0.91 (0.68-1.23)	0.5508	4 / 182 / 1057	3 / 57 / 388	1, 3, 4, 5 (n = 1319)	yes
4	123514528	*IL2-IL21*	rs4492018	A	0.24	0.21	0.88 (0.73-1.05)	0.1495	72 / 464 / 740	19 / 161 / 283	1, 3, 4, 5 (n = 1319)	yes
4	123548068	*IL21*	rs1398553	T	0.33	0.38	1.22 (1.05-1.43)	0.0109	148 / 527 / 556	69 / 225 / 183	1, 3, 4, 5 (n = 1319)	yes
5	55438580	*ANKRD55*	rs6859219	A	0.22	0.17	0.74 (0.61-0.90)	0.002953	55 / 441 / 774	14 / 131 / 320	1, 3, 4, 5 (n = 1319)	yes
5	96124330	*ERAP1*	rs30187	T	0.32	0.35	1.14 (0.97-1.34)	0.1018	139 / 510 / 574	55 / 224 / 196	1, 3, 4, 5 (n = 1319)	no
5	135287029	*LECT2*	rs31517	A	0.36	0.37	1.03 (0.88-1.20)	0.7415	166 / 561 / 514	63 / 223 / 191	1, 3, 4, 5 (n = 1319)	no
6	31540141	*LTA*	rs2239704	A	0.39	0.36	0.89 (0.75-1.05)	0.1671	131 / 386 / 324	58 / 222 / 192	1, 2, 5 (n = 869)	no
6	31540313	*LTA*	rs909253	G	0.34	0.35	1.07 (0.90-1.26)	0.4406	103 / 365 / 378	62 / 210 / 202	1, 2, 5 (n = 869)	no
6	31540784	*LTA*	rs1041981	A	0.33	0.35	1.09 (0.93-1.29)	0.2906	101 / 361 / 384	61 / 212 / 200	1, 2, 5 (n = 869)	no
6	31542482	*TNFA*	rs1799724	T	0.10	0.13	1.40 (1.09-1.79)	0.007489	11 / 145 / 691	10 / 105 / 356	1, 2, 5 (n = 869)	yes
6	31542963	*TNFA*	rs1800750	A	0.02	0.01	0.36 (0.15-0.86)	0.01635	0 / 30 / 818	0 / 6 / 465	1, 2, 5 (n = 869)	yes
6	31543031	*TNFA*	rs1800629	A	0.17	0.14	0.79 (0.63-0.99)	0.04234	29 / 228 / 591	9 / 114 / 353	1, 2, 5 (n = 869)	yes
6	31543101	*TNFA*	rs361525	A	0.05	0.03	0.55 (0.35-0.86)	0.007526	3 / 77 / 769	0 / 26 / 449	1, 2, 5 (n = 869)	yes
6	31543827	*TNFA*	rs1800610	A	0.10	0.13	1.38 (1.08-1.77)	0.009952	11 / 145 / 693	8 / 108 / 357	1, 2, 5 (n = 869)	yes

Supplementary Table S2 Allele and genotype frequencies in oligoarticular (persistent and extended) and RF negative polyarticular JIA patients versus controls

Chr	Position[a]	Gene/ region	SNP	Minor allele	MAF controls	MAF cases	OR (95% CI)	P (allelic)	Genotype counts controls	Genotype counts cases	Typed in control sets[c]	Reported JIA locus[d]
6	31544189	*TNFA*	rs3093662	G	0.06	0.04	0.75 (0.52-1.09)	0.1328	4 / 91 / 752	2 / 38 / 430	1, 2, 5 (n = 869)	yes
6	57012930	*ZNF451*	rs3734738	A	0.21	0.21	0.99 (0.82-1.19)	0.9212	53 / 428 / 772	20 / 158 / 290	1, 3, 4, 5 (n = 1319)	no
6	106568034	*PRDM1*	rs548234	C	0.32	0.35	1.13 (0.96-1.33)	0.1366	112 / 574 / 548	54 / 213 / 191	1, 3, 4, 5 (n = 1319)	no
6	138006504	*TNFAIP3*	rs6920220	A	0.21	0.20	0.98 (0.80-1.19)	0.821	41 / 269 / 538	25 / 139 / 301	1, 2, 5 (n = 869)	yes
6	159482521	*TAGAP*	rs394581	C	0.28	0.27	0.97 (0.82-1.15)	0.7544	103 / 500 / 670	33 / 188 / 246	1, 3, 4, 5 (n = 1319)	no
6	167534290	*CCR6*	rs3093023	A	0.44	0.46	1.07 (0.91-1.26)	0.3993	244 / 624 / 400	82 / 186 / 116	1, 3, 4, 5 (n = 1319)	no
7	75442759	*CCL24*	rs2302005	T	0.22	0.21	0.93 (0.78-1.12)	0.4639	55 / 400 / 703	14 / 171 / 292	1, 3, 4, 5 (n = 1319)	no
7	75442855	*CCL24*	rs2302004	C	0.44	0.42	0.94 (0.81-1.09)	0.4046	245 / 592 / 405	82 / 234 / 158	1, 3, 4, 5 (n = 1319)	no
7	92246744	*CDK6*	rs42041	G	0.26	0.25	0.95 (0.80-1.13)	0.5815	96 / 464 / 708	28 / 177 / 262	1, 3, 4, 5 (n = 1319)	no
7	128594183	*TNPO3*	rs10488631	C	0.10	0.10	1.03 (0.80-1.33)	0.8078	7 / 228 / 1023	5 / 83 / 382	1, 3, 4, 5 (n = 1319)	yes
9	34743681	*CCL21*	rs951005	C	0.15	0.16	1.08 (0.88-1.34)	0.4482	24 / 295 / 849	7 / 136 / 334	1, 3, 4, 5 (n = 1319)	no
9	139775146	*TRAF2*	rs7048473	C	0.26	0.25	0.95 (0.80-1.13)	0.5385	78 / 487 / 691	30 / 171 / 269	1, 3, 4, 5 (n = 1319)	no
9	139787453	*TRAF2*	rs2811761	G	0.21	0.21	0.99 (0.83-1.20)	0.9556	59 / 405 / 774	22 / 155 / 296	1, 3, 4, 5 (n = 1319)	no
9	139815053	*TRAF2*	rs10781522	G	0.38	0.38	1.00 (0.86-1.17)	0.9959	176 / 602 / 488	77 / 198 / 192	1, 3, 4, 5 (n = 1319)	no
9	139821068	*TRAF2*	rs3750512	C	0.38	0.37	0.96 (0.82-1.12)	0.6014	180 / 570 / 479	74 / 203 / 199	1, 3, 4, 5 (n = 1319)	no
10	6053163	*IL2RA*	rs12722605	T	0.14	0.15	1.05 (0.85-1.30)	0.6622	32 / 295 / 916	12 / 117 / 340	1, 3, 4, 5 (n = 1319)	yes
10	6099045	*IL2RA*	rs2104286	G	0.25	0.23	0.91 (0.76-1.10)	0.3382	76 / 472 / 695	29 / 139 / 252	1, 3, 4, 5 (n = 1319)	yes
10	6114660	*IL2RA*	rs41295061	A	0.09	0.09	1.02 (0.79-1.32)	0.8834	6 / 219 / 1049	4 / 78 / 384	1, 3, 4, 5 (n = 1319)	yes
10	6393260	*PRKCQ*	rs4750316	C	0.19	0.19	0.99 (0.82-1.20)	0.9552	39 / 394 / 794	16 / 148 / 306	1, 3, 4, 5 (n = 1319)	no
11	36525293	*TRAF6*	rs540386	T	0.13	0.11	0.83 (0.66-1.05)	0.1194	26 / 285 / 941	4 / 99 / 364	1, 3, 4, 5 (n = 1319)	no
11	71709272	*IL18BP*	rs3814721	C	0.06	0.07	1.18 (0.85-1.64)	0.3216	1 / 95 / 751	0 / 63 / 408	1, 2, 5 (n = 869)	no
11	71710478	*IL18BP*	rs2298455	C	0.12	0.12	0.96 (0.75-1.24)	0.7774	11 / 179 / 656	7 / 90 / 355	1, 2, 5 (n = 869)	no
11	71714078	*IL18BP*	rs1541304	T	0.03	0.02	0.87 (0.52-1.46)	0.5935	1 / 43 / 805	0 / 22 / 454	1, 2, 5 (n = 869)	no
11	112035458	*IL18*	rs1946518	T	0.40	0.40	1.00 (0.85-1.18)	0.9851	137 / 395 / 312	64 / 233 / 158	1, 2, 5 (n = 869)	no
11	117869670	*IL10RA*	rs2229113	A	0.31	0.30	0.97 (0.81-1.16)	0.7345	85 / 327 / 394	40 / 205 / 227	1, 2, 5 (n = 869)	no

Supplementary Table S2 Allele and genotype frequencies in oligoarticular (persistent and extended) and RF negative polyarticular JIA patients versus controls

Chr	Position[a]	Gene/ region	SNP	Minor allele	MAF controls	MAF cases	OR (95% CI)	P (allelic)	Genotype counts controls	Genotype counts cases	Typed in control sets[c]	Reported JIA locus[d]
12	6450945	*TNFRSF1A*	rs767455	C	0.42	0.40	0.92 (0.79-1.09)	0.3416	161 / 389 / 295	80 / 220 / 173	1, 2, 5 (n = 869)	no
12	6451590	*TNFRSF1A*	rs4149570	A	0.40	0.42	1.06 (0.90-1.25)	0.4766	151 / 377 / 315	87 / 213 / 164	1, 2, 5 (n = 869)	no
12	57968715	*KIF5A*	rs1678542	C	0.37	0.37	1.02 (0.87-1.19)	0.8226	135 / 599 / 442	66 / 217 / 184	1, 3, 4, 5 (n = 1319)	no
16	11179873	*CLEC16A*	rs12708716	G	0.35	0.33	0.92 (0.78-1.07)	0.2729	148 / 594 / 515	61 / 192 / 217	1, 3, 4, 5 (n = 1319)	yes
16	11249329	*CLEC16A*	rs6498169	G	0.34	0.37	1.09 (0.93-1.28)	0.2653	145 / 585 / 539	68 / 205 / 194	1, 3, 4, 5 (n = 1319)	yes
16	27448401	*IL21R*	rs3093341	G	0.10	0.08	0.80 (0.62-1.05)	0.1069	12 / 227 / 1005	1 / 77 / 399	1, 3, 4, 5 (n = 1319)	no
16	67189486	*TRADD*	rs11574518	T	0	0	*not polymorphic*		0 / 0 / 1143	0 / 0 / 450	1, 3, 4, 5 (n = 1319)	no
17	32594568	*CCL2-CCL7*	rs8079244	C	0	0	*not polymorphic*		0 / 0 / 1236	0 / 0 / 473	1, 3, 4, 5 (n = 1319)	no
17	40447401	*STAT5A*	rs7217728	C	0.31	0.29	0.91 (0.77-1.07)	0.2662	102 / 581 / 570	51 / 174 / 245	1, 3, 4, 5 (n = 1319)	no
17	40461003	*STAT5A*	rs2293154	A	0.18	0.18	1.05 (0.86-1.27)	0.6606	32 / 378 / 849	23 / 120 / 313	1, 3, 4, 5 (n = 1319)	no
18	67531642	*CD226*	rs763361	T	0.47	0.54	1.30 (1.12-1.51)	0.0006295	290 / 623 / 361	132 / 237 / 97	1, 3, 4, 5 (n = 1319)	no
19	44515514	*ZNF230*	rs12753	A	0.14	0.15	1.05 (0.85-1.30)	0.6291	22 / 304 / 905	10 / 121 / 346	1, 3, 4, 5 (n = 1319)	no
20	43280231	*ADA*	rs6031698	A	0	0	*not polymorphic*		0 / 0 / 844	0 / 0 / 472	1, 2, 5 (n = 869)	no
20	44746982	*CD40*	rs1883832	T	0.25	0.25	0.99 (0.82-1.19)	0.9027	57 / 306 / 484	31 / 172 / 273	1, 2, 5 (n = 869)	no
21	34640788	*IL10RB*	rs2834167	G	0.24	0.27	1.14 (0.95-1.37)	0.1566	61 / 293 / 494	39 / 174 / 254	1, 2, 5 (n = 869)	no
22	24236392	*MIF*	rs755622	C	0.21	0.15	0.67 (0.54-0.83)	0.0002084	37 / 283 / 526	10 / 121 / 334	1, 2, 5 (n = 869)	yes
22	37544245	*IL2RB*	rs3218258	T	0.28	0.27	0.97 (0.82-1.15)	0.7135	99 / 514 / 655	31 / 196 / 243	1, 3, 4, 5 (n = 1319)	yes
22	37544810	*IL2RB*	rs3218253	T	0.28	0.28	0.99 (0.84-1.17)	0.9164	98 / 506 / 652	33 / 195 / 242	1, 3, 4, 5 (n = 1319)	yes
22	37551607	*IL2RB*	rs743777	G	0.34	0.33	0.95 (0.81-1.12)	0.5386	143 / 552 / 543	43 / 225 / 207	1, 3, 4, 5 (n = 1319)	yes

Chr: chromosome; MAF: minor allele frequency; OR: odds ratio; CI: confidence interval

a) Base-pair position is based on NCBI dbSNP build 136

b) 11: homozygous for the minor allele; 12: heterozygous; 22: homozygous for the major allele

c) See supplementary Table S1 for details of control sets

d) See Table 2 for references

All presented results are derived from analyses with the homogeneous patient group (persistent or extended oligoarticular and RF negative polyarticular JIA) compared to controls.

Supplementary Table S3 Allele frequencies and associations per JIA subgroup versus controls

Gene/region	SNP	Minor allele	Controls n = 869 / 1319[a]	JIA homogeneous[b] (n = 493) vs controls			Persistent oligoarthritis (n = 263) vs controls			Extented oligoarthritis (n = 88) vs controls			RF negative polyarthritis (n = 142) vs controls			ANA positive JIA[c] (n = 254) vs controls		
			MAF	MAF	OR	p	MAF	OR	p	MAF	OR	p	MAF	OR	p	MAF	OR	p
TNFRSF14-MMEL1	rs3890745	G	0.32	0.30	0.90	0.2137	0.31	0.92	0.4347	0.29	0.85	0.347	0.30	0.90	0.4611	0.28	0.83	0.08291
TNFRSF8-MIIP	rs946461	T	0.26	0.29	1.15	0.09358	0.26	0.99	0.9563	0.33	1.40	0.0428	0.32	1.32	0.04465	0.30	1.20	0.09404
TNFRSF1B	rs1061622	G	0.23	0.24	1.03	0.7678	0.23	1.00	0.9709	0.22	0.91	0.6237	0.26	1.17	0.2849	0.26	1.16	0.2131
LCK	rs1004420	T	0.17	0.17	0.98	0.8087	0.18	1.03	0.8286	0.17	0.98	0.9097	0.16	0.88	0.4721	0.17	0.96	0.7445
LCK	rs695161	C	0.48	0.47	0.97	0.6721	0.46	0.94	0.5339	0.50	1.09	0.6046	0.47	0.95	0.6838	0.45	0.90	0.2833
PTPN22	rs2476601	A	0.10	0.13	1.32	0.02702	0.11	1.08	0.6468	0.14	1.51	0.07322	0.16	1.67	0.00493	0.13	1.39	0.03457
VTCN1	rs6673837	A	0.20	0.20	0.99	0.9474	0.21	1.07	0.5881	0.19	0.90	0.5935	0.19	0.92	0.6078	0.21	1.03	0.8411
VTCN1	rs2358817	T	0.08	0.07	0.88	0.4164	0.08	1.00	0.9886	0.08	1.00	0.9936	0.05	0.61	0.0817	0.08	0.94	0.7407
VTCN1	rs2358820	A	0.07	0.07	0.92	0.602	0.08	1.07	0.7114	0.07	0.96	0.8891	0.04	0.61	0.1135	0.07	1.06	0.7725
VTCN1	rs10923217	C	0.48	0.52	1.21	0.02079	0.51	1.12	0.2585	0.49	1.07	0.6787	0.58	1.50	0.002179	0.52	1.20	0.07851
VTCN1	rs6669320	A	0.15	0.13	0.89	0.3117	0.13	0.88	0.4157	0.13	0.83	0.4585	0.14	0.92	0.6767	0.14	0.94	0.6633
VTCN1	rs10923223	C	0.15	0.16	1.09	0.4383	0.17	1.21	0.1692	0.16	1.08	0.7348	0.13	0.89	0.5622	0.18	1.28	0.07157
VTCN1	rs12046117	T	0.13	0.13	1.04	0.7252	0.14	1.11	0.473	0.14	1.07	0.7836	0.12	0.90	0.6181	0.16	1.26	0.1072
PTPRC	rs10919563	A	0.13	0.11	0.86	0.195	0.12	0.96	0.7804	0.10	0.76	0.2868	0.10	0.73	0.1446	0.12	0.94	0.6871
IL10	rs1800896	C	0.50	0.47	0.90	0.2119	0.47	0.88	0.2208	0.45	0.82	0.2266	0.50	1.00	1	0.49	0.94	0.5658
IL19	rs2243191	T	0.20	0.23	1.17	0.1209	0.21	1.10	0.4737	0.25	1.36	0.1071	0.23	1.19	0.2811	0.22	1.15	0.2677
IL20	rs1400986	T	0.16	0.14	0.86	0.1975	0.16	0.98	0.857	0.17	1.04	0.8427	0.10	0.57	0.007092	0.15	0.90	0.4437
AFF3	rs1160542	G	0.45	0.46	1.05	0.5177	0.44	0.95	0.6405	0.52	1.35	0.06018	0.47	1.07	0.582	0.46	1.06	0.5746
AFF3	rs10865035	A	0.46	0.47	1.05	0.5762	0.45	0.97	0.7889	0.54	1.37	0.08522	0.47	1.03	0.8378	0.47	1.04	0.7041
IL18RAP	rs917997	T	0.22	0.24	1.14	0.1782	0.23	1.07	0.5657	0.27	1.34	0.1124	0.24	1.15	0.3743	0.25	1.17	0.1966
IL1A	rs17561	A	0.30	0.29	0.92	0.3289	0.29	0.91	0.4294	0.29	0.94	0.7177	0.28	0.90	0.4967	0.28	0.90	0.3559

Supplementary Table S3 Allele frequencies and associations per JIA subgroup versus controls (continued)

Gene/region	SNP	Minor allele	Controls n = 869 / 1319[a]	JIA homogeneous[b] (n = 493) vs controls			Persistent oligoarthritis (n = 263) vs controls			Extented oligoarthritis (n = 88) vs controls			RF negative polyarthritis (n = 142) vs controls			ANA positive JIA[c] (n = 254) vs controls		
			MAF	MAF	OR	p	MAF	OR	p	MAF	OR	p	MAF	OR	p	MAF	OR	p
IL1A	rs1800587	A	0.31	0.28	0.89	0.2285	0.29	0.95	0.6497	0.25	0.74	0.1427	0.28	0.89	0.4431	0.27	0.84	0.1471
IL1B	rs1143634	A	0.25	0.24	0.95	0.5542	0.23	0.92	0.5044	0.23	0.89	0.5441	0.25	1.02	0.8818	0.23	0.91	0.4422
IL1B	rs16944	A	0.33	0.35	1.11	0.2315	0.33	1.01	0.9639	0.39	1.32	0.09227	0.37	1.18	0.2235	0.35	1.12	0.3072
DPP4	rs2268894	C	0.45	0.47	1.07	0.4192	0.47	1.06	0.5513	0.41	0.86	0.3464	0.50	1.24	0.105	0.46	1.04	0.6856
STAT1	rs3771300	C	0.48	0.50	1.10	0.2321	0.47	0.96	0.7153	0.51	1.15	0.3818	0.55	1.35	0.01999	0.48	1.02	0.8538
STAT1	rs13010343	A	0.14	0.13	0.96	0.7449	0.14	0.99	0.9477	0.12	0.86	0.5314	0.14	0.98	0.9254	0.15	1.09	0.5533
STAT1	rs1547550	C	0.35	0.34	0.95	0.5685	0.35	0.98	0.8245	0.34	0.93	0.6744	0.33	0.93	0.5853	0.34	0.97	0.744
STAT1	rs7562024	T	0.40	0.39	0.95	0.5502	0.39	0.95	0.6424	0.43	1.14	0.4157	0.36	0.85	0.2286	0.40	1.01	0.9559
CD28	rs1980422	C	0.22	0.27	1.29	0.008079	0.26	1.23	0.09935	0.27	1.30	0.1918	0.29	1.39	0.03501	0.30	1.52	0.0004481
CTLA4	rs231775	G	0.37	0.35	0.92	0.3251	0.35	0.90	0.3164	0.36	0.94	0.716	0.36	0.95	0.6931	0.35	0.92	0.4572
CCR5	rs333	del	0.10	0.08	0.81	0.1168	0.09	0.83	0.2842	0.06	0.57	0.08363	0.09	0.92	0.721	0.09	0.86	0.3884
FAM107A	rs13315591	C	0.07	0.08	1.13	0.3795	0.08	1.15	0.4292	0.06	0.90	0.7552	0.09	1.25	0.3376	0.09	1.30	0.1396
4p15	rs874040	G	0.31	0.29	0.93	0.3556	0.27	0.84	0.09887	0.36	1.28	0.1325	0.28	0.90	0.4424	0.30	0.95	0.6689
KIAA1109	rs4505848	G	0.36	0.40	1.20	0.01901	0.38	1.13	0.2286	0.41	1.26	0.1603	0.42	1.31	0.03709	0.40	1.20	0.07744
ADAD1	rs11732095	G	0.08	0.07	0.91	0.5508	0.07	0.90	0.6068	0.04	0.48	0.07923	0.09	1.20	0.4245	0.07	0.96	0.8327
IL2-IL21	rs4492018	A	0.24	0.21	0.88	0.1495	0.20	0.81	0.08452	0.25	1.05	0.8018	0.22	0.89	0.4681	0.22	0.92	0.4964
IL21	rs1398553	T	0.33	0.38	1.22	0.0109	0.38	1.21	0.05882	0.40	1.31	0.0934	0.38	1.20	0.178	0.38	1.25	0.03146
ANKRD55	rs6859219	A	0.22	0.17	0.74	0.002953	0.18	0.81	0.09507	0.19	0.84	0.3994	0.14	0.57	0.002153	0.16	0.69	0.005596
ERAP1	rs30187	T	0.32	0.35	1.14	0.1018	0.34	1.09	0.4044	0.36	1.19	0.2774	0.36	1.20	0.163	0.35	1.12	0.2729
LECT2	rs31517	A	0.36	0.37	1.03	0.7415	0.37	1.05	0.6601	0.34	0.93	0.6575	0.37	1.06	0.6833	0.36	1.02	0.8649
LTA	rs2239704	A	0.39	0.36	0.89	0.1671	0.38	0.98	0.8285	0.30	0.68	0.02545	0.35	0.88	0.3353	0.37	0.94	0.5656

Supplementary Table S3 Allele frequencies and associations per JIA subgroup versus controls (continued)

Gene/region	SNP	Minor allele	Controls n = 869 / 1319[a]	JIA homogeneous[b] (n = 493) vs controls			Persistent oligoarthritis (n = 263) vs controls			Extented oligoarthritis (n = 88) vs controls			RF negative polyarthritis (n = 142) vs controls			ANA positive JIA[c] (n = 254) vs controls		
			MAF	MAF	OR	p	MAF	OR	p	MAF	OR	p	MAF	OR	p	MAF	OR	p
LTA	rs909253	G	0.34	0.35	1.07	0.4406	0.34	1.01	0.9397	0.39	1.25	0.1703	0.35	1.07	0.617	0.37	1.13	0.2434
LTA	rs1041981	A	0.33	0.35	1.09	0.2906	0.34	1.04	0.7436	0.40	1.33	0.08439	0.35	1.07	0.6184	0.37	1.16	0.1618
TNFA	rs1799724	T	0.10	0.13	1.40	0.007489	0.13	1.39	0.03609	0.13	1.39	0.1626	0.14	1.43	0.06627	0.15	1.58	0.002279
TNFA	rs1800750	A	0.02	0.01	0.36	0.01635	0.01	0.34	0.06219	0.01	0.65	0.5485	0.00	0.20	0.08317	0.00	0.23	0.02768
TNFA	rs1800629	A	0.17	0.14	0.79	0.04234	0.12	0.68	0.01005	0.15	0.87	0.5175	0.16	0.97	0.8566	0.14	0.80	0.1244
TNFA	rs361525	A	0.05	0.03	0.55	0.007526	0.03	0.52	0.02582	0.04	0.83	0.6328	0.02	0.44	0.04588	0.02	0.36	0.002901
TNFA	rs1800610	A	0.10	0.13	1.38	0.009952	0.13	1.42	0.02286	0.13	1.31	0.2737	0.13	1.37	0.1157	0.15	1.61	0.001418
TNFA	rs3093662	G	0.06	0.04	0.75	0.1328	0.04	0.75	0.2412	0.05	0.88	0.7177	0.04	0.67	0.2213	0.03	0.55	0.02543
ZNF451	rs3734738	A	0.21	0.21	0.99	0.9212	0.21	0.97	0.8117	0.23	1.12	0.5601	0.20	0.95	0.7468	0.22	1.06	0.622
PRDM1	rs548234	C	0.32	0.35	1.13	0.1366	0.33	1.05	0.644	0.38	1.28	0.1353	0.36	1.19	0.1948	0.36	1.20	0.0787
TNFAIP3	rs6920220	A	0.21	0.20	0.98	0.821	0.19	0.92	0.5275	0.22	1.08	0.7053	0.21	1.02	0.8938	0.20	0.98	0.8617
TAGAP	rs394581	C	0.28	0.27	0.97	0.7544	0.28	1.00	0.9931	0.28	1.00	0.9958	0.26	0.91	0.5282	0.27	0.97	0.7971
CCR6	rs3093023	A	0.44	0.46	1.07	0.3993	0.47	1.12	0.3127	0.44	1.01	0.9509	0.45	1.04	0.7957	0.43	0.98	0.8225
CCL24	rs2302005	T	0.22	0.21	0.93	0.4639	0.19	0.86	0.2088	0.23	1.06	0.7666	0.22	1.00	0.9886	0.21	0.93	0.5674
CCL24	rs2302004	C	0.44	0.42	0.94	0.4046	0.38	0.81	0.03051	0.49	1.27	0.1343	0.44	1.02	0.8712	0.42	0.95	0.642
CDK6	rs42041	G	0.26	0.25	0.95	0.5815	0.26	1.02	0.8385	0.26	1.00	0.9918	0.22	0.80	0.15	0.25	0.95	0.6539
TNPO3	rs10488631	C	0.10	0.10	1.03	0.8078	0.11	1.15	0.3883	0.09	0.98	0.9295	0.08	0.85	0.498	0.10	1.10	0.5706
CCL21	rs951005	C	0.15	0.16	1.08	0.4482	0.17	1.15	0.2895	0.15	1.02	0.9258	0.15	1.00	0.992	0.17	1.17	0.2316
TRAF2	rs7048473	C	0.26	0.25	0.95	0.5385	0.25	0.97	0.8145	0.24	0.89	0.5493	0.24	0.93	0.6308	0.25	0.95	0.6402
TRAF2	rs2811761	G	0.21	0.21	0.99	0.9556	0.21	0.98	0.8389	0.20	0.93	0.7283	0.22	1.07	0.6615	0.23	1.11	0.3989
TRAF2	rs10781522	G	0.38	0.38	1.00	0.9959	0.38	1.03	0.7762	0.37	0.99	0.9326	0.37	0.96	0.7444	0.39	1.06	0.5554

Supplementary Table S3 Allele frequencies and associations per JIA subgroup versus controls (continued)

Gene/region	SNP	Minor allele	Controls n = 869 / 1319[a]	JIA homogeneous[b] (n = 493) vs controls			Persistent oligoarthritis (n = 263) vs controls			Extented oligoarthritis (n = 88) vs controls			RF negative polyarthritis (n = 142) vs controls			ANA positive JIA[c] (n = 254) vs controls		
			MAF	MAF	OR	p	MAF	OR	p	MAF	OR	p	MAF	OR	p	MAF	OR	p
TRAF2	rs3750512	C	0.38	0.37	0.96	0.6014	0.37	0.96	0.6644	0.37	0.96	0.7817	0.37	0.97	0.7972	0.38	1.03	0.7936
IL2RA	rs12722605	T	0.14	0.15	1.05	0.6622	0.16	1.11	0.4539	0.15	1.07	0.7598	0.14	0.93	0.6884	0.15	1.06	0.6882
IL2RA	rs2104286	G	0.25	0.23	0.91	0.3382	0.24	0.94	0.582	0.19	0.71	0.09939	0.25	1.02	0.9141	0.23	0.92	0.4751
IL2RA	rs41295061	A	0.09	0.09	1.02	0.8834	0.09	0.98	0.8898	0.10	1.14	0.6107	0.09	1.02	0.9163	0.09	1.00	0.993
PRKCQ	rs4750316	C	0.19	0.19	0.99	0.9552	0.18	0.93	0.5832	0.21	1.13	0.5353	0.20	1.03	0.8562	0.22	1.15	0.2461
TRAF6	rs540386	T	0.13	0.11	0.83	0.1194	0.12	0.84	0.2368	0.11	0.83	0.4601	0.11	0.82	0.3398	0.11	0.76	0.08008
IL18BP	rs3814721	C	0.06	0.07	1.18	0.3216	0.07	1.18	0.4299	0.07	1.33	0.3517	0.06	1.09	0.7532	0.07	1.31	0.1792
IL18BP	rs2298455	C	0.12	0.12	0.96	0.7774	0.12	1.03	0.856	0.13	1.06	0.817	0.10	0.80	0.3006	0.13	1.07	0.6699
IL18BP	rs1541304	T	0.03	0.02	0.87	0.5935	0.02	0.74	0.4001	0.02	0.86	0.7822	0.03	1.11	0.798	0.02	0.76	0.4337
IL18	rs1946518	T	0.40	0.40	1.00	0.9851	0.42	1.11	0.3339	0.38	0.94	0.7224	0.36	0.86	0.2847	0.39	0.95	0.6597
IL10RA	rs2229113	A	0.31	0.30	0.97	0.7345	0.28	0.89	0.2876	0.34	1.17	0.353	0.31	1.01	0.9266	0.32	1.03	0.7612
TNFRSF1A	rs767455	C	0.42	0.40	0.92	0.3416	0.42	0.99	0.9141	0.37	0.82	0.2178	0.39	0.88	0.3469	0.39	0.89	0.2598
TNFRSF1A	rs4149570	A	0.40	0.42	1.06	0.4766	0.43	1.12	0.2806	0.43	1.12	0.484	0.39	0.93	0.5849	0.41	1.05	0.6677
KIF5A	rs1678542	C	0.37	0.37	1.02	0.8226	0.35	0.92	0.4395	0.42	1.25	0.1688	0.39	1.07	0.6106	0.37	0.99	0.8935
CLEC16A	rs12708716	G	0.35	0.33	0.92	0.2729	0.36	1.01	0.9414	0.36	1.02	0.8991	0.28	0.70	0.01183	0.31	0.82	0.05822
CLEC16A	rs6498169	G	0.34	0.37	1.09	0.2653	0.35	1.01	0.9101	0.37	1.10	0.5513	0.40	1.25	0.09136	0.38	1.18	0.1082
IL21R	rs3093341	G	0.10	0.08	0.80	0.1069	0.07	0.72	0.0696	0.10	1.04	0.8741	0.08	0.82	0.3732	0.08	0.77	0.1394
TRADD	rs11574518	T	0	0	Not polymorphic													
CCL2-CCL7	rs8079244	C		0	Not polymorphic													
STAT5A	rs7217728	C	0.31	0.29	0.91	0.2662	0.27	0.83	0.08635	0.28	0.86	0.3998	0.34	1.12	0.4273	0.30	0.94	0.5391
STAT5A	rs2293154	A	0.18	0.18	1.05	0.6606	0.18	1.00	0.9989	0.21	1.23	0.302	0.18	1.02	0.9117	0.19	1.11	0.4299

Supplementary Table S3 Allele frequencies and associations per JIA subgroup versus controls (continued)

Gene/region	SNP	Minor allele	Controls n = 869 / 1319[a]	JIA homogeneous[b] (n = 493) vs controls			Persistent oligoarthritis (n = 263) vs controls			Extented oligoarthritis (n = 88) vs controls			RF negative polyarthritis (n = 142) vs controls			ANA positive JIA[c] (n = 254) vs controls		
			MAF	MAF	OR	p	MAF	OR	p	MAF	OR	p	MAF	OR	p	MAF	OR	p
CD226	rs763361	T	0.47	0.54	1.30	0.0006295	0.55	1.39	0.0008022	0.52	1.23	0.194	0.51	1.19	0.1818	0.53	1.27	0.01752
ZNF230	rs12753	A	0.14	0.15	1.05	0.6291	0.15	1.09	0.549	0.20	1.53	0.03052	0.11	0.73	0.1149	0.17	1.26	0.07806
ADA	rs6031698	A	0	0	Not polymorphic													
CD40	rs1883832	T	0.25	0.25	0.99	0.9027	0.24	0.95	0.6524	0.22	0.88	0.4875	0.27	1.14	0.3614	0.24	0.97	0.8199
IL10RB	rs2834167	G	0.24	0.27	1.14	0.1566	0.28	1.21	0.09756	0.21	0.83	0.339	0.28	1.23	0.1563	0.27	1.12	0.3515
MIF	rs755622	C	0.21	0.15	0.67	0.0002084	0.18	0.82	0.1387	0.11	0.47	0.002125	0.13	0.53	0.0009787	0.15	0.66	0.002712
IL2RB	rs3218258	T	0.28	0.27	0.97	0.7135	0.26	0.92	0.4651	0.23	0.76	0.1478	0.32	1.22	0.1579	0.25	0.84	0.1144
IL2RB	rs3218253	T	0.28	0.28	0.99	0.9164	0.27	0.96	0.69	0.23	0.77	0.1579	0.32	1.22	0.1449	0.25	0.85	0.1534
IL2RB	rs743777	G	0.34	0.33	0.95	0.5386	0.32	0.91	0.3628	0.30	0.82	0.2601	0.37	1.12	0.3797	0.30	0.85	0.1258

MAF: minor allele frequency; RF: rheumatoid factor; ANA: antinuclear antibodies

a) Typed control sets per SNP are listed in Supplementary Table S2

b) Including oligoarthritis (persistent and extended) and RF negative polyarthritis patients

c) Including persistent oligoarthritis (n=129), extended oligoarthritis (n=60), and RF negative polyarthritis (n=65) patients

Supplementary Table S4
Meta-analyses of reported JIA loci*

SNP (minor allele)							
PTPN22 rs2476601 (1858) (A)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{\text{meta-analysis}}$
Viken 2005	Norway	320	555	*A-allele associated with disease, but data to calculate allelic OR not available*			
Hinks 2005	UK	661	595	17%	1.53	(1.2 - 2)	
Seldin 2005	Finland	230	1400	5%	1.17	(0.9 - 1.5)	
Cinek 2006	Czech Republic	130	400	7%	2.35	(1.61 - 3.42)	
Pazár 2008	Hungary	150	200	3%	1.13	(0.66 - 1.95)	
Thompson 2010	USA, Germany, Czech Republic	949	1214	27%	1.67	(1.38 - 2.01)	
Ellis 2013	Australia	200	341	5%	1.45	(0.93 - 2.27)	
Dimopoulou 2013	Greece	128	221	2%	2.23	(1.03 - 4.84)	
Kaalla 2013	USA (overlap not reported)	636	733	18%	1.29	(1.02 - 1.62)	
Reinards et al.	*present study*			16%	1.32	(1.03 - 1.69)	
pooled					**1.50**		**8.95E-16**
VTCN1 rs6673837 (A)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{\text{meta-analysis}}$
Hinks 2009 II	UK	654	1847	35%	1.16	(1 - 1.37)	
Thompson 2012	USA	810	3040	43%	0.95	(0.82 - 1.09)	
Reinards et al.	*present study*			22%	0.99	(0.82 - 1.21)	
pooled					1.03		0.5485
VTCN1 rs2358817 (T)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{\text{meta-analysis}}$
Hinks 2009 II	UK	654	1847	27%	0.68	(0.52 - 0.89)	
Thompson 2012	USA	812	3056	51%	1.12	(0.92 - 1.36)	
Reinards et al.	*present study*			22%	0.88	(0.65 - 1.19)	
pooled					0.93		0.3035

Supplementary Table S4 (continued)
Meta-analyses of reported JIA loci*

SNP (minor allele)							
VTCN1 rs2358820 (A)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{\text{meta-analysis}}$
Hinks 2009 II	UK discovery	249	184	10%	0.40	(0.23 - 0.68)	
	UK validation	321	2024	9%	0.45	(0.26 - 0.78)	
Thompson 2012	USA	814	3058	58%	1.10	(0.9 - 1.36)	
Reinards et al.	*present study*			24%	0.92	(0.67 - 1.26)	
pooled					0.88		0.1227
VTCN1 rs10923217 (C)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{\text{meta-analysis}}$
Hinks 2009 II	UK	654	1847	59%	1.17b	(1.02 - 1.33)	
Reinards et al.	*present study*			41%	1.21	(1.03 - 1.42)	
pooled					**1.19**		**0.001113**
VTCN1 rs6669320 (A)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{\text{meta-analysis}}$
Hinks 2009 II	UK	654	1847	62%	0.80	(0.67 - 0.97)	
Reinards et al.	*present study*			38%	0.89	(0.7 - 1.12)	
pooled					**0.83**		**0.01299**
VTCN1 rs10923223 (C)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{\text{meta-analysis}}$
Hinks 2009 II	UK	654	1847	58%	1.45	(1.2 - 1.75)	
Reinards et al.	*present study*			42%	1.09	(0.88 - 1.36)	
pooled					**1.29**		**0.0005872**
VTCN1 rs12046117 (T)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{\text{meta-analysis}}$
Hinks 2009 II	UK	654	1847	48%	1.58	(1.29 - 1.94)	
Ellis 2013	Australia	200	341	16%	1.15	(0.81 - 1.64)	
Reinards et al.	*present study*			36%	1.04	(0.82 - 1.32)	
pooled					**1.29**		**0.0003681**

Supplementary Table S4 (continued)
Meta-analyses of reported JIA loci*

SNP (minor allele)							
PTPRC rs10919563 (A)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	p $_{meta\text{-}analysis}$
Hinks 2012	UK, USA	1611[a]	12719[a]	80%	0.88	(0.78 - 0.99)	
Thompson 2012	USA	*overlap with Hinks 2012*					
Reinards et al.	*present study*			20%	0.86	(0.68 - 1.08)	
pooled					**0.88**		**0.01388**
AFF3 rs1160542 (G)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	p $_{meta\text{-}analysis}$
Hinks 2010 II	UK	915	2967	40%	1.25	(1.13 - 1.39)	
Thompson 2012	USA	810	3054	34%	1.11	(0.99 - 1.24)	
Ellis 2013	Australia	200	341	7%	1.16	(0.91 - 1.49)	
Reinards et al.	*present study*			19%	1.05	(0.9 - 1.22)	
pooled					**1.16**		**1.31E-05**
CTLA4 rs231775 (+49) (G)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	p $_{meta\text{-}analysis}$
Miterski 2004	Germany	197	362	13%	0.92	(0.71 - 1.19)	
Suppiah 2005	UK (Northern Ireland)	72	475	7%	0.76	(0.53 - 1.09)	
Prahalad 2008	USA (>90% of Northern European ancestry)	650	345	25%	0.95	(0.79 - 1.15)	
Thompson 2010	USA, UK	809[a]	3521[a]	22%	0.98	(0.84 - 1.15)	
Reinards et al.	*present study*			32%	0.92	(0.78 - 1.09)	
pooled					0.93		0.1224
CCR5 rs333 (delta32) (del)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	p $_{meta\text{-}analysis}$
Lindner 2007	Norway	515	645	22%	0.82	(0.63 - 1.07)	
Hinks 2010 III	UK	983	3121	56%	0.79	(0.66 - 0.94)	
Reinards et al.	*present study*			22%	0.81	(0.62 - 1.06)	
pooled					**0.80**		**0.0005273**

Supplementary Table S4 (continued)
Meta-analyses of reported JIA loci*

SNP (minor allele)							
TNFA rs1799724 (-857) (T)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{\text{meta-analysis}}$
Zeggini 2002 II	UK	*no evidence of association with disease, but no exact data available*					
Miterski 2004	Germany	170	415	28%	1.10	(0.74 - 1.63)	
Reinards et al.	*present study*			72%	1.40	(1.09 - 1.79)	
pooled					**1.31**		**0.01207**
TNFA rs1800629 (-308) (A)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{\text{meta-analysis}}$
Ozen 2002	Czech Republic	159	100	8%	1.48	(0.94 - 2.33)	
Zeggini 2002 II	UK	138	75	5%	2.12	(1.2 - 3.7)	
Miterski 2004	Germany	122	312	10%	1.13	(0.76 - 1.68)	
Schmeling 2006	Germany (overlap not reported)	228	196	11%	0.78	(0.53 - 1.13)	
Cimaz 2007	France (cases and controls), Italy (cases)	107	630	*no evidence of association with disease, but no exact data available*			
Mourão 2009	Portugal	114	117	*no significant differences between cases and controls, but data to calculate allelic OR not available*			
Kaalla 2013	USA	628	729	35%	0.82	(0.66 - 1.01)	
Reinards et al.	*present study*			32%	0.79	(0.63 - 0.99)	
pooled					0.91		0.1609
TNFA rs361525 (-238) (A)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{\text{meta-analysis}}$
Ozen 2002	Czech Republic	159	100	22%	2.02	(1.28 - 3.19)	
Zeggini 2002 II	UK	137	76	6%	0.41	(0.17 - 0.95)	
Miterski 2004	Germany	130	375	6%	0.71	(0.29 - 1.77)	
Schmeling 2006	Germany (overlap not reported)	228	196	7%	1.30	(0.58 - 2.93)	
Cimaz 2007	France (cases and controls), Italy (cases)	107	630	*no evidence of association with disease, but no exact data available*			
Kaalla 2013	USA	638	749	35%	0.66	(0.46 - 0.95)	
Reinards et al.	*present study*			23%	0.55	(0.35 - 0.86)	
pooled					0.83		0.08965

Supplementary Table S4 (continued)
Meta-analyses of reported JIA loci*

SNP (minor allele)							
TNFAIP3 rs6920220 (A)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	p $_{\text{meta-analysis}}$
Prahalad 2009	USA (>90% of Northern European ancestry)	441	619	15%	1.30	(1.05 - 1.61)	
Hinks 2010	UK	873	3644	42%	1.16	(1.02 - 1.31)	
Thompson 2010	USA (overlap not reported)	809[a]	531[a]	19%	0.94	(0.78 - 1.13)	
Thompson 2012	USA	*overlap with Thompson 2010*					
Ellis 2013	Australia	200	341	7%	1.04	(0.77 - 1.41)	
Reinards et al.	*present study*			17%	0.98	(0.8 - 1.19)	
pooled					**1.09**		**0.03309**
TNPO3 rs10488631 (C)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	p $_{\text{meta-analysis}}$
Hinks 2012	UK	1179	5176	78%	1.20	(1.05 - 1.37)	
Reinards et al.	*present study*			22%	1.03	(0.8 - 1.33)	
pooled					**1.16**		**0.01277**
IL2RA rs2104286 (G)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	p $_{\text{meta-analysis}}$
Hinks 2009	UK	593	>3000a	20%	0.76	(0.66 - 0.88)	
Prahalad 2009	USA (>90% of Northern European ancestry)	438	634	11%	1.04	(0.85 - 1.27)	
Thompson 2010 initial cohort	USA, UK (overlap not reported)	809a	3521a	25%	0.76	(0.66 - 0.86)	
Thompson 2010 replication cohort	USA, Germany, Czech Republic (overlap not reported)	1015a	1569a	26%	0.96	(0.84 - 1.1)	
Thompson 2012	USA	*overlap with Thompson 2010*					
Ellis 2013	Australia	200	341	5%	0.87	(0.64 - 1.18)	
Reinards et al.	*present study*			13%	0.91	(0.76 - 1.1)	
pooled					**0.86**		**8.21E-06**

Supplementary Table S4 (continued)
Meta-analyses of reported JIA loci*

SNP (minor allele)							
IL2RA rs41295061 (A)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{meta\text{-}analysis}$
Hinks 2009	UK	619	3614	58%	0.80	(0.63 - 1)	
Reinards et al.	*present study*			42%	1.02	(0.79 - 1.32)	
pooled					0.89		0.1646
CLEC16A rs12708716 (G)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{meta\text{-}analysis}$
Skinningsrud 2010	Norway	507	2109	36%	0.89	(0.77 - 1.03)	
Thompson 2010	USA	809[a]	531[a]	31%	0.98	(0.84 - 1.16)	
Thompson 2012	USA	*overlap with Thompson 2010*					
Reinards et al.	*present study*			33%	0.92	(0.78 - 1.07)	
pooled					0.93		0.09463
CLEC16A rs6498169 (G)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{meta\text{-}analysis}$
Skinningsrud 2010	Norway	498	2110	28%	1.19	(1.03 - 1.37)	
Thompson 2012	USA	814	3056	41%	1.11	(0.99 - 1.25)	
Ellis 2013	Australia	200	341	8%	1.03	(0.79 - 1.33)	
Reinards et al.	*present study*			23%	1.09	(0.93 - 1.28)	
pooled					**1.12**		**0.002768**
MIF rs755622 (-173) (C)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{meta\text{-}analysis}$
Donn 2002	UK	526	259	15%	1.86	(1.36 - 2.55)	
Miterski 2004	Germany	150	390	14%	1.21	(0.88 - 1.66)	
Kaalla 2013	USA	638	742	39%	1.06	(0.88 - 1.29)	
Reinards et al.	*present study*			32%	0.67	(0.54 - 0.83)	
pooled					1.01		0.8222

Supplementary Table S4 (continued)
Meta-analyses of reported JIA loci*

SNP (minor allele)							
IL2RB rs743777 (G)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{\text{meta-analysis}}$
Thompson 2012	USA	812	3051	67%	1.02	(0.91 - 1.14)	
Reinards et al.	*present study*			33%	0.95	(0.81 - 1.12)	
pooled					1.00		0.9405
IL1B rs1143634 (3954) (A)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{\text{meta-analysis}}$
Cimaz 2007	France (cases+controls), Italy (cases)	107	630	*A-allele protective for disease, but exact data not available*			
Reinards et al.	*present study*				0.95	(0.79 - 1.14)	
no meta-analysis performed							
TNFA rs1800750 (-376) (A)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{\text{meta-analysis}}$
Zeggini 2002 II	UK	*no evidence of association with disease, but no exact data available*					
Reinards et al.	*present study*				0.36	(0.15 - 0.86)	
no meta-analysis performed							

OR: odds ratio; CI: confidence interval
Patient group of the present study limited to oligoarticular (persistent and extended) and RF negative JIA patients References are listed in Supplementary Table S6.s
a) Exact number of succesfully typed individuals not known
b) Minor allele unclear

Supplementary Table S5

Meta-analyses of loci previously tested in JIA (but not significantly associated*)

SNP (minor allele)							
CD28 rs1980422 (C)[b]	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{meta\text{-}analysis}$
Thompson 2012	USA	814	3058	69%	1.14	(1 - 1.29)	
Reinards et al.	*present study*			31%	1.29	(1.07 - 1.55)	
pooled					**1.18**		**0.001411**
CD226 rs763361 (T)[b]	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{meta\text{-}analysis}$
Hinks 2010 II	UK	600	3494	53%	1.07	(0.94 - 1.21)	
Ellis 2013	Australia	158	341	11%	1.22	(0.93 - 1.59)	
Reinards et al.	*present study*			36%	1.30	(1.12-1.51)	
pooled					**1.16**		**0.001115**
TNFRSF14-MMEL1 rs3890745 (G)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{meta\text{-}analysis}$
Thompson 2010	USA, UK	809[a]	3521[a]	63%	0.92	(0.81 - 1.04)	
Thompson 2012	USA	*overlap with Thompson 2010*					
Reinards et al.	*present study*			37%	0.90	(0.77 - 1.06)	
pooled					**0.91**		**0.07282**
TNFRSF1B rs1061622 (G)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{meta\text{-}analysis}$
Zeggini 2002	UK	435	261	35%	1.25	(0.97 - 1.61)	
Reinards et al.	*present study*			65%	1.03	(0.85 - 1.24)	
pooled					**1.10**		**0.2057**
LCK rs695161 (C)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{meta\text{-}analysis}$
Thompson 2012	USA	813	3057	64%	0.98	(0.88 - 1.1)	
Reinards et al.	*present study*			36%	0.97	(0.83 - 1.13)	
pooled					**0.98**		**0.5911**

Supplementary Table S5 (continued)

Meta-analyses of loci previously tested in JIA (but not significantly associated*)

SNP (minor allele)							
IL10 rs1800896 (-1082) (C)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{\text{meta-analysis}}$
Crawley 1999	UK	435	274	28%	1.07	(0.86 - 1.32)	
Donn 2001	UK (overlap not reported)	348	239	24%	0.83	(0.66 - 1.05)	
Reinards et al.	*present study*			48%	0.90	(0.77 - 1.06)	
pooled					**0.93**		**0.1908**
IL18RAP rs917997 (T)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{\text{meta-analysis}}$
Hinks 2010 IV	UK	987	2931	71%	1.00	(0.89 - 1.13)	
Reinards et al.	*present study*			29%	1.14	(0.94 - 1.37)	
pooled					**1.04**		**0.4693**
IL1A rs1800587 (-889) (A)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{\text{meta-analysis}}$
McDowell 1995	Norway	269	99	6%	1.34	(0.94 - 1.9)	
Donn 2001	UK	330	236	11%	0.75	(0.57 - 0.97)	
Cinek 2004	Czech Republic	130	102	4%	1.19	(0.78 - 1.81)	
Thompson 2012	USA	814	3058	55%	1.04	(0.93 - 1.18)	
Reinards et al.	*present study*			23%	0.89	(0.74 - 1.07)	
pooled					**0.99**		**0.825**
IL1B rs16944 (-511) (A)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{\text{meta-analysis}}$
Cinek 2004	Czech Republic	130	103	14%	1.29	(0.86 - 1.95)	
Reinards et al.	*present study*			86%	1.11	(0.94 - 1.31)	
pooled					**1.13**		**0.116**

Supplementary Table S5 (continued)
Meta-analyses of loci previously tested in JIA (but not significantly associated*)

SNP (minor allele)							
STAT1 rs7562024 (T)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{\text{meta-analysis}}$
Thompson 2012	USA	814	3058	67%	1.00	(0.9 - 1.12)	
Reinards et al.	*present study*			33%	0.95	(0.82 - 1.11)	
pooled					**0.98**		**0.7298**
FAM107A rs13315591 (C)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{\text{meta-analysis}}$
Thompson 2012	USA	814	3056	64%	0.92	(0.75 - 1.14)	
Reinards et al.	*present study*			36%	1.13	(0.86 - 1.5)	
pooled					**0.99**		**0.9204**
4p15 rs874040 (G)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{\text{meta-analysis}}$
Thompson 2012	USA	811	3057	67%	1.03	(0.92 - 1.16)	
Reinards et al.	*present study*			33%	0.93	(0.79 - 1.09)	
pooled					**0.99**		**0.9008**
ERAP1 rs30187 (T)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{\text{meta-analysis}}$
Hinks 2011	UK	1054[a]	5200[a]	71%	1.02	(0.92 - 1.13)	
Ellis 2013	Australia	200	341	8%	1.06	(0.82 - 1.37)	
Reinards et al.	*present study*			21%	1.14	(0.97 - 1.34)	
pooled					**1.05**		**0.2089**
LECT2 rs31517 (T)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{\text{meta-analysis}}$
Thompson 2012	USA	814	3057	65%	0.92	(0.82 - 1.03)	
Reinards et al.	*present study*			35%	1.03	(0.88 - 1.2)	
pooled					**0.96**		**0.3354**

Supplementary Table S5 (continued)
Meta-analyses of loci previously tested in JIA (but not significantly associated*)

SNP (minor allele)							
PRDM1 rs548234 (C)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{meta\text{-}analysis}$
Hinks 2012	UK	1170	8001	43%	0.96	(0.88 - 1.06)	
Thompson 2012	USA	813	3056	37%	1.03	(0.92 - 1.16)	
Reinards et al.	*present study*			20%	1.13	(0.96 - 1.33)	
pooled					**1.02**		0.6309
TAGAP rs394581 (C)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{meta\text{-}analysis}$
Hinks 2012	UK	1175	2617	70%	1.00	(0.9 - 1.12)	
Reinards et al.	*present study*			30%	0.97	(0.82 - 1.15)	
pooled					**0.99**		0.8646
CCR6 rs3093023 (A)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{meta\text{-}analysis}$
Hinks 2012	UK	1002	8128	49%	0.96	(0.87 - 1.05)	
Thompson 2012	USA	806	3047	35%	1.08	(0.97 - 1.21)	
Reinards et al.	*present study*			16%	1.07	(0.91 - 1.26)	
pooled					**1.02**		0.5788
CDK6 rs42041 (G)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{meta\text{-}analysis}$
Hinks 2010	UK	926	2962	53%	1.03	(0.92 - 1.16)	
Thompson 2010	USA, UK (overlap not reported)	809[a]	3521[a]	27%	0.99	(0.87 - 1.13)	
Thompson 2012	USA	*overlap with Thompson 2010*					
Reinards et al.	*present study*			20%	0.95	(0.8 - 1.13)	
pooled					**1.00**		0.9404

Supplementary Table S5 (continued)

Meta-analyses of loci previously tested in JIA (but not significantly associated*)

SNP (minor allele)							
CCL21 rs951005 (C)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{meta-analysis}$
Hinks 2012	UK	999	7947	72%	0.91	(0.8 - 1.04)	
Reinards et al.	*present study*			28%	1.08	(0.88 - 1.34)	
pooled					**0.96**		**0.43**
PRKCQ rs4750316 (C)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{meta-analysis}$
Hinks 2010	UK	943	3500	42%	0.88	(0.77 - 1)	
Thompson 2012	USA	814	3058	33%	0.87	(0.75 - 1)	
Ellis 2013	Australia	200	341	6%	0.88	(0.63 - 1.23)	
Reinards et al.	*present study*			19%	0.99	(0.82 - 1.2)	
pooled					**0.90**		**0.01012**
TRAF6 rs540386 (T)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{meta-analysis}$
Thompson 2012	USA	814	3051	69%	1.10	(0.94 - 1.28)	
Reinards et al.	*present study*			31%	0.83	(0.66 - 1.05)	
pooled					**1.01**		**0.8841**
TNFRSF1A rs767455 (C)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{meta-analysis}$
Hinks 2013	UK	987	5194	74%	0.98	(0.89 - 1.08)	
Reinards et al.	*present study*			26%	0.92	(0.79 - 1.09)	
pooled					**0.97**		**0.4013**
TNFRSF1A rs4149570 (A)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{meta-analysis}$
Thompson 2012	USA	812	3055	37%	1.02	(0.91 - 1.14)	
Hinks 2013	UK	929	5191	46%	0.94	(0.85 - 1.04)	
Reinards et al.	*present study*			18%	1.06	(0.9 - 1.25)	
pooled					**0.99**		**0.7597**

Supplementary Table S5 (continued)

Meta-analyses of loci previously tested in JIA (but not significantly associated*)

SNP (minor allele)							
KIF5A rs1678542 (C)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{meta\text{-}analysis}$
Hinks 2010	UK	941	3530	42%	0.91	(0.82 - 1.01)	
Thompson 2010	USA, UK	809[a]	3521[a]	33%	1.00	(0.89 - 1.13)	
Thompson 2012	USA	*overlap with Thompson 2010*					
Ellis 2013	Australia	200	341	7%	0.96	(0.74 - 1.24)	
Reinards et al.	*present study*			19%	1.02	(0.87 - 1.19)	
pooled					**0.96**		**0.2652**
IL21R rs3093341 (G)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{meta\text{-}analysis}$
Thompson 2012	USA	814	3057	66%	0.99	(0.82 - 1.2)	
Reinards et al.	*present study*			34%	0.80	(0.62 - 1.05)	
pooled					**0.92**		**0.3058**
STAT5A rs7217728 (C)	origin	nr of cases	nr of controls	weight	OR	(95% CI)	$p_{meta\text{-}analysis}$
Thompson 2012	USA	812	3058	65%	0.96	(0.85 - 1.08)	
Reinards et al.	*present study*			35%	0.91	(0.77 - 1.07)	
pooled					**0.94**		**0.2319**

OR: odds ratio; CI: confidence interval

* Patient group of the present study limited to oligoarticular (persistent and extended) and RF-negative JIA patients References are listed in Supplementary Table S6

a) Exact number of succesfully typed individuals not known

b) Patient group of all included studies limited to oligoarticular (persistent and extended) and RF-negative JIA patients

SupplementaryTable S6. References of studies analysed for meta-analysis (supplementary Tables S4 and S5)

Cimaz 2007[1]	Cimaz R, Cazalis MA, Reynaud C et al. IL1 and TNF gene polymorphisms in patients with juvenile idiopathic arthritis treated with TNF inhibitors. *Ann Rheum Dis 2007; 66(7):900-904.*
Cinek 2004[2]	Cinek O, Vavrincova P, Striz I et al. Association of single nucleotide polymorphisms within cytokine genes with juvenile idiopathic arthritis in the Czech population. *J Rheumatol 2004; 31(6):1206-1210.*
Cinek 2006[3]	Cinek O, Hradsky O, Ahmedov G et al. No independent role of the -1123 G>C and+2740 A>G variants in the association of PTPN22 with type 1 diabetes and juvenile idiopathic arthritis in two Caucasian populations. *Diabetes Res Clin Pract 2007; 76(2):297-303.*
Crawley 1999[4]	Crawley E, Kay R, Sillibourne J et al. Polymorphic haplotypes of the interleukin-10 5' flanking region determine variable interleukin-10 transcription and are associated with particular phenotypes of juvenile rheumatoid arthritis. *Arthritis Rheum 1999; 42(6):1101-1108.*
Dimopoulou 2013[5]	Dimopoulou DG, Zervou MI, Trachana M et al. Investigation of juvenile idiopathic arthritis susceptibility loci: results from a Greek population. *Hum Immunol* 2013; 74(9):1194-1198.
Donn 2001[6]	Donn RP, Barrett JH, Farhan A et al. Cytokine gene polymorphisms and susceptibility to juvenile idiopathic arthritis. British Paediatric Rheumatology Study Group. *Arthritis Rheum* 2001; 44(4):802-810.
Donn 2002[7]	Donn R, Alourfi Z, De BF et al. Mutation screening of the macrophage migration inhibitory factor gene: positive association of a functional polymorphism of macrophage migration inhibitory factor with juvenile idiopathic arthritis. *Arthritis Rheum* 2002; 46(9):2402-2409.
Ellis 2013[8]	Ellis JA, Chavez RA, Pezic A et al. Independent replication analysis of genetic loci with previous evidence of association with juvenile idiopathic arthritis. *Pediatr Rheumatol Online J* 2013; 11(1):12.
Hinks 2005[9]	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(6):1694-1699.
Hinks 2009[10]	Hinks A, Ke X, Barton A et al. Association of the IL2RA/CD25 gene with juvenile idiopathic arthritis. *Arthritis Rheum* 2009; 60(1):251-257.
Hinks 2009 II[11]	Hinks A, Barton A, Shephard N et al. Identification of a novel susceptibility locus for juvenile idiopathic arthritis by genome-wide association analysis. *Arthritis Rheum* 2009; 60(1):258-263.
Hinks 2010[12]	Hinks A, Eyre S, Ke X et al. Overlap of disease susceptibility loci for rheumatoid arthritis and juvenile idiopathic arthritis. *Ann Rheum Dis* 2010; 69(6):1049-1053.
Hinks 2010 II[13]	Hinks A, Eyre S, Ke X et al. Association of the AFF3 gene and IL2/IL21 gene region with juvenile idiopathic arthritis. *Genes Immun* 2010; 11(2):194-198.
Hinks 2010 III[14]	Hinks A, Martin P, Flynn E et al. Association of the CCR5 gene with juvenile idiopathic arthritis. *Genes Immun* 2010; 11(7):584-589.
Hinks 2010 IV[15]	Hinks A, Martin P, Flynn E et al. Investigation of type 1 diabetes and coeliac disease susceptibility loci for association with juvenile idiopathic arthritis. *Ann Rheum Dis* 2010; 69(12):2169-2172.
Hinks 2011[16]	Hinks A, Martin P, Flynn E et al. Subtype specific genetic associations for juvenile idiopathic arthritis: ERAP1 with the enthesitis related arthritis subtype and IL23R with juvenile psoriatic arthritis. *Arthritis Res Ther* 2011; 13(1):R12.
Hinks 2012[17]	Hinks A, Cobb J, Sudman M et al. Investigation of rheumatoid arthritis susceptibility loci in juvenile idiopathic arthritis confirms high degree of overlap. *Ann Rheum Dis* 2012; 71(7):1117-1121.
Hinks 2013[18]	Hinks A, Martin P, Thompson SD et al. Autoinflammatory gene polymorphisms and susceptibility to UK juvenile idiopathic arthritis. *Pediatr Rheumatol Online J* 2013; 11(1):14.

Kaalla 2013[19]	Kaalla MJ, Broadaway KA, Rohani-Pichavant M et al. Meta-analysis confirms association between TNFA-G238A variant and JIA, and between PTPN22-C1858T variant and oligoarticular, RF-polyarticular and RF-positive polyarticular JIA. *Pediatr Rheumatol Online J* 2013; 11(1):40.
Lindner 2007[20]	Lindner E, Nordang GB, Melum E et al. Lack of association between the chemokine receptor 5 polymorphism CCR5delta32 in rheumatoid arthritis and juvenile idiopathic arthritis. *BMC Med Genet* 2007; 8:33.
McDowell 1995[21]	McDowell TL, Symons JA, Ploski R et al. A genetic association between juvenile rheumatoid arthritis and a novel interleukin-1 alpha polymorphism. *Arthritis Rheum* 1995; 38(2):221-228.
Miterski 2004[22]	Miterski B, Drynda S, Boschow G et al. Complex genetic predisposition in adult and juvenile rheumatoid arthritis. *BMC Genet* 2004; 5:2.
Mourão 2009[23]	Mourao AF, Caetano-Lopes J, Costa P et al. Tumor necrosis factor-alpha -308 genotypes influence inflammatory activity and TNF-alpha serum concentrations in children with juvenile idiopathic arthritis. *J Rheumatol* 2009; 36(4):837-842.
Ozen 2002[24]	Ozen S, Alikasifoglu M, Bakkaloglu A et al. Tumour necrosis factor alpha G-->A -238 and G-->A -308 polymorphisms in juvenile idiopathic arthritis. *Rheumatology (Oxford)* 2002; 41(2):223-227.
Pazár 2008[25]	Pazar B, Gergely P, Jr., Nagy ZB et al. Role of HLA-DRB1 and PTPN22 genes in susceptibility to juvenile idiopathic arthritis in Hungarian patients. *Clin Exp Rheumatol* 2008; 26(6):1146-1152.
Prahalad 2008[26]	Prahalad S, Bohnsack JF, Whiting A et al. Lack of association of functional CTLA4 polymorphisms with juvenile idiopathic arthritis. *Arthritis Rheum* 2008; 58(7):2147-2152.
Prahalad 2009[27]	Prahalad S, Hansen S, Whiting A et al. Variants in TNFAIP3, STAT4, and C12orf30 loci associated with multiple autoimmune diseases are also associated with juvenile idiopathic arthritis. *Arthritis Rheum* 2009; 60(7):2124-2130.
Schmeling 2006[28]	Schmeling H, Wagner U, Peterson A et al. Tumor necrosis factor alpha promoter polymorphisms in patients with juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2006; 24(1):103-108.
Seldin 2005[29]	Seldin MF, Shigeta R, Laiho K et al. Finnish case-control and family studies support PTPN22 R620W polymorphism as a risk factor in rheumatoid arthritis, but suggest only minimal or no effect in juvenile idiopathic arthritis. *Genes Immun* 2005; 6(8):720-722.
Skinningsrud 2010[30]	Skinningsrud B, Lie BA, Husebye ES et al. A CLEC16A variant confers risk for juvenile idiopathic arthritis and anti-cyclic citrullinated peptide antibody negative rheumatoid arthritis. *Ann Rheum Dis* 2010; 69(8):1471-1474.
Suppiah 2005[31]	Suppiah V, O'doherty C, Heggarty S et al. The CTLA4+49A/G and CT60 polymorphisms and chronic inflammatory arthropathies in Northern Ireland. *Exp Mol Pathol* 2006; 80(2):141-146.
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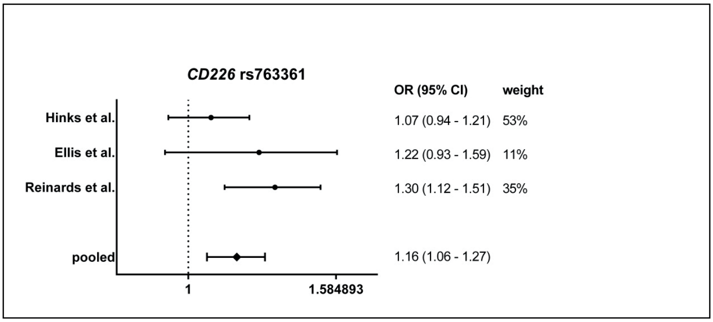
Supplementary Figure S1 Meta-analysis of novel JIA susceptibility loci

a. Meta-analysis of *CD226* rs763361, restricted to oligoarticular and RF negative JIA patients of Caucasian origin



b. Meta-analysis of *CD28* rs1980422, restricted to oligoarticular and RF negative JIA patients of Caucasian origin