

Supplementary Information

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Patient information

The post quality control (QC) United States (US) cohort comprised 222 US RF-positive polyarticular JIA patients and 4408 US controls. Clinics enrolling at least 5 JIA patients for Cincinnati-based studies (listed in order of number contributed) were located in Cincinnati, OH; Atlanta, GA; Columbus, OH; Little Rock, AR; Long Island, NY; Charlotte, NC; Cleveland, OH; Chicago, IL; Dover, DE; Nashville, TN; Philadelphia, PA; Milwaukee, WI; Toledo, OH; Charleston, SC; and Indianapolis, IN. Additional DNA from JIA cases collected independently by investigators in Salt Lake City, UT, Dallas, TX, Kansas City, MO and Boston, MA or enrolled as part of the Trial of Early Aggressive Therapy in Juvenile Idiopathic Arthritis (TREAT) study (clinical trials identifier NCT00443430) were made available for genotyping in Cincinnati.

The US controls were derived from four sources: healthy children without known major health conditions recruited from the geographical area served by Cincinnati Children's Hospital Medical Center (CCHMC) and healthy adults collected at CCHMC. Healthy adult controls from Utah screened for autoimmune diseases and all were included in the replication cohort of previous GWAS studies[1;2]. Healthy adult controls collected at the Oklahoma Medical Research Foundation; and healthy US adult controls from the Genotype and Phenotype registry (www.gapregistry.org) and the NIDDK IBD Genetics Consortium. Healthy controls from the Oklahoma Medical Research Foundation (OMRF) were provided by the Lupus Family Registry and Repository (LFRR)[3] and the Oklahoma Immune Cohort (OIC). Each individual completed the Connective Tissue Disease Screening Questionnaire (CSQ)[4] and individuals with a "probable" systemic rheumatic disease were excluded. Each individual was enrolled into these studies after appropriate written consent and IRB approval by the OMRF and the University of Oklahoma Health Sciences Center. Healthy controls were also provided from the University of Minnesota SLE sibship collection[5] and these subjects were enrolled after appropriate written consent and IRB approval by the University of Minnesota. The US collections and their use in genetic studies have been approved by the Institutional Review Board of CCHMC and each collaborating center.

The post QC United Kingdom (UK) cohort comprised 94 RF-positive polyarticular JIA patients from five sources: The British Society for Paediatric and Adolescent Rheumatology (BSPAR) National Repository of JIA; a cohort of UK patients with long-standing JIA, described previously[6]; a cohort collected as part of the Childhood Arthritis Prospective Study (CAPS), a prospective inception cohort study of JIA cases from 5 centers across UK[7]; a cohort of children recruited for the SPARKS-CHARM (Childhood Arthritis Response to Medication) study, who fulfil ILAR criteria for JIA and are about to start new disease-modifying medication for active arthritis[8] and an ongoing collection of UK cases, the UK JIA Genetics Consortium (UKJIAGC). JIA cases were classified according to ILAR criteria[9]. There

is overlap in the JIA cases used in this study and in previous UK candidate gene studies of JIA^[10-13]. All UK JIA cases were recruited with ethical approval and provided informed consent [North-West Multi-Centre Research Ethics Committee (MREC 99/8/84), the University of Manchester Committee on the Ethics of Research on Human Beings and National Research Ethics Service (NRES 02/8/104)]. The UK controls comprised the shared UK 1958 Birth cohort and UK Blood Services Common Controls. The collection was established as part of the WTCCC[14].

The post QC German cohort comprised 1 German RF-positive polyarticular JIA patient and 480 controls. These cases have already been included as a replication cohort in a genome-wide association study and previously described. These patients were recruited from the German Center for Rheumatology in Children and Adolescents, Garmisch-Partenkirchen; the Department of Pediatrics, University of Tübingen; Children's Rheumatology Unit Sendenhorst, Germany; and the Department of Pediatrics, University of Prague, Czech Republic. JIA was determined retrospectively by chart review. German population-based control samples were prepared from cord blood obtained from healthy newborns in the Survey of Neonates in Pomerania (SNiP) consortium[15]. The respective Institutional Review Boards approved the collection of these samples and participation in this study.

The post QC Norwegian cohort comprised 13 Norwegian RF-positive polyarticular JIA patients and 945 controls. The patient cohort comprised consecutive cases of JIA from two defined geographical areas in Norway with disease onset from 2000-2012 and with available DNA samples. The study was an extended part of the Nordic JIA Study, a prospective, multicentre cohort study initiated by NoSPeR (Nordic Study group of Pediatric Rheumatology) as previously described[16]. The cohort aimed to be as close to population-based as possible, as centres participated only if they were able to include all children diagnosed with JIA in their catchment area. Approval from medical and health research ethical committees and data authorities were granted and informed consent obtained from parents and/or children according to national regulations. The Norwegian controls were from the second (1995-1997) or third (2006-2008) waves of the population-based Nord-Trøndelag Health Study (HUNT) (www.ntnu.edu/hunt). They were a random selection of participants who had answered "no" to questions of whether they had ever been given a diagnosis of rheumatoid arthritis or ankylosing spondylitis. All HUNT participants gave written, informed consent. The study was approved by the Regional Committee for Medical and Health Research Ethics, Central Norway, the Norwegian Data Inspectorate, and the Norwegian Department of Health.

The post QC Canadian Cohort comprised 10 Canadian RF-positive polyarticular JIA patients. The BBOP study (Biologically Based Outcome Predictors in JIA) is a multi-center inception cohort of

prospectively collected children with new onset JIA recruited from 11 Canadian Pediatric Rheumatology Programs. Children were included in the study if they satisfied the ILAR classification criteria, were within six months of disease onset, and were treatment-naïve for medications except for non-steroidal anti-inflammatory agents. Peripheral blood and saliva samples were collected and processed as per standardized protocol at enrolment and transported to the central biobank (The Hospital for Sick Children (SickKids), Toronto, ON). Informed consent for participation was obtained from parents and informed consent or assent was obtained from patients as applicable. The study was approved by the Research Ethics Board at each participating site.

Supplementary Table 1 Samples used in the wGRS analyses

	Cases	Controls
RF-positive polyarticular JIA	Total 340	Total 10147
	UK=94	UK=4337*
	US=222	US=4386
	Germany=1	Germany=480
	Norway=13	Norway=945
	Canada=10	
Early-onset RA (16-29 yrs)	UK=370	UK=4338 [#]
Later-onset RA (≥70 yrs)	UK=259	UK=4338 [#]

*These 4337 UK controls are unique compared to the #4338 used in the RA analysis.

Supplementary Table 2 Association results in RF-positive polyarticular JIA of the 27 non-HLA SNPs most strongly associated with RF-negative polyarticular and oligoarticular JIA

SNP	Chr	Position	Gene Region	RF-poJIA minor allele	RF-poJIA risk allele	reference allele	MAF RF- poJIA	MAF controls	MAF RF+pJIA	RF-poJIA OR	RF-poJIA CI	best p-value RF+pJIA	Model	RF+pJIA OR	RF+pJIA CI
rs4648881	1	25197155	<i>RUNX3</i>	G	G	G	0.47	0.49	0.51	1.16	1.1-1.23	0.91	add	1.01	0.87-1.18
rs6679677	1	114303808	<i>PTPN22</i>	A	A	A	0.14	0.10	0.15	1.59	1.45-1.73	1.21E-06	dom	1.83	1.43-2.33
rs11265608	1	154364140	<i>ATP8B2 IL6R</i>	A	A	A	0.12	0.10	0.12	1.28	1.16-1.4	0.17	add	1.18	0.93-1.49
rs6740838	2	100813499	<i>AFF3 LONRF2</i>	A	A	A	0.43	0.39	0.42	1.25	1.14-1.37	0.20	add	1.11	0.95-1.29
rs10174238	2	191973034	<i>STAT4</i>	G	G	G	0.28	0.23	0.27	1.29	1.2-1.37	0.08	add	1.17	0.98-1.39
rs79893749	3	46253650	<i>CCR1 CCR3</i>	A	G	A	0.12	0.15	0.11	0.79	0.72-0.86	0.009	add	0.72	0.56-0.92
rs4688013	3	119229486	<i>TIMMDC1 CD80</i>	A	A	A	0.22	0.19	0.17	1.20	1.12-1.29	0.16	add	0.86	0.7-1.06
rs1479924	4	123387600	<i>IL2 IL21</i>	G	A	G	0.24	0.29	0.29	0.80	0.74-0.85	0.91	add	1.01	0.85-1.2
rs71624119	5	55440730	<i>ANKRD55</i>	A	G	A	0.20	0.25	0.19	0.78	0.73-0.84	0.003	add	0.74	0.61-0.9
rs27290	5	96350088	<i>ERAP2 LNPEP</i>	G	G	G	0.47	0.44	0.43	1.32	1.2-1.45	0.98	add	1.00	0.86-1.16
rs4705862	5	131813219	<i>C5orf56 IRF1</i>	T	A	T	0.39	0.44	0.43	0.84	0.79-0.89	0.78	add	0.98	0.84-1.14
rs7808122	7	22798080	<i>IL6</i>	A	A	A	0.48	0.44	0.41	1.18	1.11-1.25	0.46	add	0.94	0.81-1.1
rs10280937	7	28182306	<i>JAZF1</i>	G	G	G	0.13	0.11	0.11	1.25	1.14-1.37	0.82	add	0.97	0.76-1.24
rs7909519	10	6089841	<i>IL2RA</i>	C	A	C	0.08	0.11	0.08	0.72	0.64-0.8	0.08	add	0.78	0.6-1.03
rs7069750	10	90762376	<i>FAS</i>	C	C	C	0.48	0.44	0.43	1.18	1.11-1.25	0.74	add	0.97	0.83-1.14
rs4755450	11	36363575	<i>PRR5L</i>	A	G	A	0.31	0.35	0.33	0.85	0.8-0.91	0.37	add	0.93	0.79-1.09
rs2364480	12	6495275	<i>LTBR</i>	C	C	C	0.28	0.25	0.24	1.20	1.12-1.28	0.31	add	0.91	0.76-1.09
rs3184504	12	111884608	<i>SH2B3 ATXN2</i>	A	A	A	0.54	0.49	0.53	1.20	1.13-1.27	0.01	add	1.22	1.04-1.42
rs7993214	13	40350912	<i>COG6</i>	A	G	A	0.31	0.35	0.32	0.84	0.79-0.9	0.23	add	0.91	0.77-1.07
rs34132030	13	43056036	<i>13q14</i>	A	A	A	0.32	0.29	0.31	1.18	1.11-1.26	0.13	add	1.14	0.96-1.34
rs12434551	14	69253364	<i>ZFP36L1</i>	A	T	A	0.43	0.47	0.45	0.85	0.8-0.9	0.30	add	0.92	0.79-1.07
rs66718203	16	11428643	<i>PRM1 RMI2</i>	C	G	C	0.14	0.18	0.14	0.81	0.74-0.88	0.006	add	0.73	0.58-0.91

rs2847293	18	12782448	<i>PTPN2</i>	A	A	A	0.20	0.17	0.18	1.31	1.22-1.4	0.32	add	1.11	0.91-1.36
rs34536443	19	10463118	<i>TYK2</i>	G	C	G	0.03	0.05	0.02	0.56	0.47-0.67	0.01	add	0.53	0.33-0.88
rs9979383	21	36715761	<i>RUNX1</i>	G	A	G	0.33	0.37	0.39	0.78	0.72-0.85	0.37	add	1.07	0.92-1.26
rs2266959	22	21922904	<i>UBE2L3</i>	A	A	A	0.22	0.19	0.21	1.24	1.15-1.33	0.41	add	1.08	0.9-1.31
rs2284033	22	37534034	<i>IL2RB</i>	A	G	A	0.39	0.44	0.43	0.84	0.79-0.89	0.70	add	0.97	0.83-1.13

RF-poJIA=RF-negative polyarticular and oligoarticular JIA, RF+pJIA=RF-positive polyarticular JIA, Chr=chromosome, SNP=single nucleotide polymorphism, MAF=minor allele frequency, dom=dominant, add=additive, OR=odds ratio, CI=confidence interval. Regions with p-value <0.05 are highlighted in bold.

Supplementary Table 3 Association results in RF-positive polyarticular JIA of the 44 non-HLA SNPs most strongly associated with RA

SNP	Chr	Position	Gene region	RA risk allele	RF+ pJIA ref allele	MAF RF+ pJIA	MAF controls	RA OR	RF+ pJIA best pvalue	Model	OR	CI
rs2843401	1	2517993	<i>MMEL1</i>	A	A	0.27	0.33	0.87	5.05E-04	add	0.74	0.62-0.87
rs2240336	1	17546989	<i>PADI4</i>	A	A	0.38	0.42	0.88	1.96E-02	add	0.83	0.71-0.97
rs883220	1	38389458	<i>POU3F1</i>	A	A	0.24	0.25	0.89	6.05E-01	add	0.95	0.8-1.14
rs2476601	1	114179091	<i>PTPN22</i>	A	A	0.15	0.1	1.78	1.30E-06	dom	1.83	1.43-2.33
rs798000	1	117082219	<i>CD2</i>	G	G	0.33	0.32	1.11	3.85E-01	add	1.07	0.91-1.26
rs8192284	1	152693594	<i>IL6R</i>	C	C	0.36	0.41	0.9	1.68E-02	add	0.82	0.7-0.97
rs10494360	1	159742374	<i>FCGR2A</i>	G	A	0.11	0.12	1.14	2.48E-01	add	0.86	0.67-1.11
rs2014863	1	197076224	<i>PTPRC</i>	C	G	0.38	0.37	1.09	4.77E-01	add	1.06	0.9-1.24
rs34695944	2	60978354	<i>REL</i>	G	G	0.37	0.37	1.13	4.30E-01	add	1.07	0.91-1.25
rs6546146	2	65409828	<i>SPRED2</i>	A	A	0.37	0.37	0.9	7.49E-01	add	0.97	0.83-1.14
rs10209110	2	100039124	<i>AFF3</i>	A	A	0.49	0.5	0.9	6.46E-01	add	0.96	0.83-1.12
rs13426947	2	191641499	<i>STAT4</i>	A	A	0.22	0.19	1.15	9.22E-02	add	1.17	0.97-1.42
rs11571302	2	204451179	<i>CTLA4</i>	A	A	0.43	0.47	0.89	2.41E-02	add	0.84	0.72-0.98
rs1980422	2	204318641	<i>CD28</i>	G	G	0.27	0.23	1.12	2.36E-02	add	1.22	1.03-1.45
rs35677470	3	58158676	<i>DNASE1L3</i>	A	A	0.08	0.08	1.19	9.51E-01	add	1.01	0.76-1.35
rs932036	4	25699960	<i>RBPJ</i>	A	T	0.33	0.3	1.14	4.29E-02	add	1.18	1.01-1.39
rs78560100	4	123260921	<i>IL2-IL21</i>	C	C	0.08	0.07	1.13	3.94E-01	add	1.13	0.85-1.5
rs71624119	5	55476487	<i>ANKRD55</i>	A	A	0.19	0.24	0.81	2.91E-03	add	0.74	0.61-0.9
rs39984	5	102625191	<i>GIN1</i>	A	A	0.29	0.32	0.88	1.15E-01	add	0.87	0.73-1.03
rs6911690	6	106577656	<i>PRDM1</i>	G	G	0.11	0.11	0.87	8.16E-01	add	0.97	0.76-1.24
rs6920220	6	138048197	<i>TNFAIP3</i>	A	A	0.25	0.22	1.2	4.42E-03	add	1.29	1.08-1.54
rs629326	6	159416701	<i>TAGAP</i>	C	C	0.4	0.41	0.9	4.65E-01	add	0.94	0.81-1.1
rs59466457	6	167457744	<i>CCR6</i>	A	A	0.51	0.44	1.15	4.37E-04	add	1.32	1.13-1.54
rs3807306	7	128367916	<i>IRF5</i>	C	A	0.56	0.49	0.89	6.46E-04	add	1.31	1.12-1.53

rs4840565	8	11382954	BLK	G	G	0.34	0.27	1.1	5.31E-04	add	1.33	1.13-1.57
rs2812378	9	34700260	CCL21	G	G	0.38	0.34	1.15	5.87E-02	add	1.16	0.99-1.36
rs10739580	9	122735103	TRAF1	G	G	0.35	0.35	1.12	8.86E-01	add	1.01	0.86-1.19
rs10795791	10	6148346	IL2RA	G	G	0.46	0.41	1.09	2.02E-02	add	1.2	1.03-1.4
rs947474	10	6430456	PRKCQ	G	G	0.18	0.19	0.9	9.14E-01	add	0.99	0.81-1.2
rs2275806	10	8135346	GATA3	G	G	0.48	0.43	1.11	2.36E-02	add	1.19	1.02-1.39
rs12764378	10	63470010	ARID5B	A	A	0.25	0.22	1.14	1.06E-01	add	1.16	0.97-1.38
rs570676	11	36448767	TRAF6	A	A	0.38	0.39	0.93	4.80E-01	add	0.94	0.81-1.11
rs595158	11	60666157	CD5	C	A	0.51	0.5	1.09	6.51E-01	add	1.04	0.89-1.21
rs4938573	11	118247052	DDX6	G	G	0.15	0.19	0.87	3.44E-03	add	0.72	0.58-0.9
rs8043085	15	36615432	RASGRP1	A	A	0.23	0.24	1.17	3.67E-01	add	0.92	0.77-1.1
rs8026898	15	67778471	TLE3	A	A	0.31	0.27	1.17	2.09E-02	add	1.22	1.03-1.44
rs13330176	16	84576588	IRF8	A	A	0.27	0.23	1.15	7.74E-02	add	1.17	0.98-1.39
rs12936409	17	35297175	IKZF3	A	A	0.48	0.47	1.1	2.54E-01	add	1.09	0.94-1.28
rs34536443	19	10324118	TYK2	G	G	0.02	0.05	0.62	1.36E-02	add	0.53	0.33-0.88
rs6032662	20	44167717	CD40	G	G	0.23	0.25	0.86	4.28E-01	add	0.93	0.77-1.12
rs2834512	21	34833469	RCAN1	A	A	0.11	0.12	0.86	2.58E-01	add	0.87	0.68-1.11
rs9979383	21	35637631	RUNX1	G	G	0.39	0.37	0.9	3.71E-01	add	1.07	0.92-1.26
rs3218251	22	35875451	IL2RB	A	A	0.29	0.26	1.13	3.88E-02	add	1.19	1.01-1.41
rs13397*	23	153248248	IRAK1	A	A	0.18	0.12	1.27	1.49E-02	add	1.37	

This list does not include *HLA* and *KIF5A* region, the latter is a deletion polymorphism and not analysed in this study.

RF-poJIA=RF-negative polyarticular and oligoarticular JIA, RF+pJIA=RF-positive polyarticular JIA, Chr=chromosome, SNP=single nucleotide polymorphism, MAF=minor allele frequency, dom=dominant, add=additive, OR=odds ratio, CI=confidence interval.

* MAF for this SNP is for females only. The p-value and OR are from the meta-analysis of females and male cohorts. Regions with p-value <0.05 are highlighted in bold.

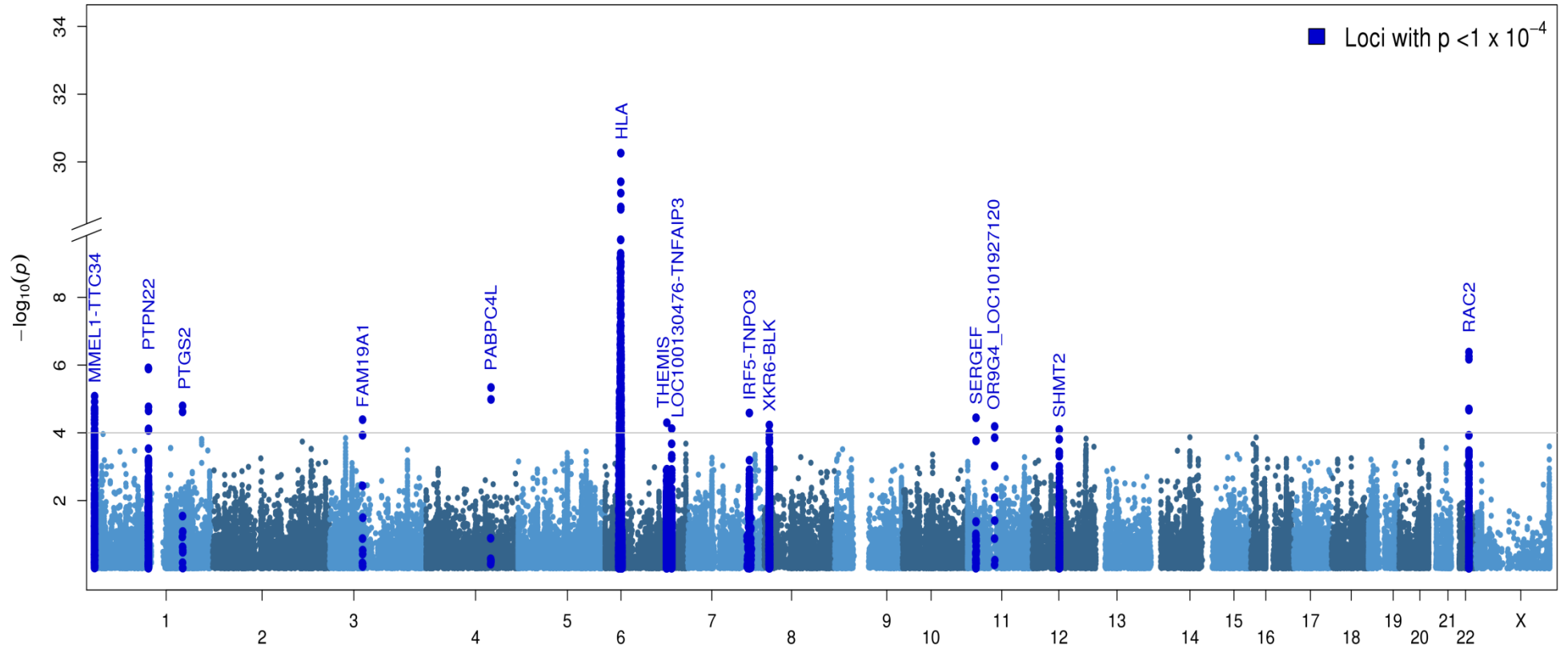
Supplementary Table 4 Most significant associations in RF-positive polyarticular JIA

Gene Region	Most Significant		Ref. Allele	RAF Cases	RAF Controls	P value	Model	OR (95% CI)	SNP Location	
	SNP	Chr								Position ^a
<i>MMEL1-TTC34</i>	rs7526311	1	2697298	T	0.50	0.43	1.21 x 10 ⁻⁵	Dominant	1.81 (1.39-2.35)	INTERGENIC
<i>PTPN22</i>	rs6679677	1	114303808	A	0.15	0.10	1.21 x 10 ⁻⁶	Dominant	1.83 (1.43-2.33)	INTERGENIC
<i>PTGS2</i>	rs6681231	1	186659859	C	0.22	0.16	1.60 x 10 ⁻⁵	Additive	1.51 (1.25-1.81)	INTERGENIC
<i>PTGS2</i>	rs20432 ^b	1	186646323	C	0.21	0.15	7.13 x 10 ⁻⁶	Additive	1.63 (1.32-2.02)	INTRON
<i>FAM19A1</i>	rs7617075	3	68240106	T	0.14	0.20	4.09 x 10 ⁻⁵	Dominant	0.59 (0.46-0.76)	INTRON
<i>PABPC4L</i>	rs970036	4	135040295	G	0.47	0.43	4.59 x 10 ⁻⁶	Recessive	1.78 (1.39-2.28)	INTERGENIC
<i>THEMIS</i>	rs62425513	6	128077738	T	0.22	0.16	5.03 x 10 ⁻⁵	Additive	1.47 (1.22-1.78)	INTRON
<i>LOC100130476-TNFAIP3</i>	rs610366	6	138139694	G	0.09	0.15	7.52 x 10 ⁻⁵	Dominant	0.56 (0.42-0.75)	INTERGENIC
<i>IRF5-TNPO3</i>	rs4731531	7	128562647	A	0.54	0.46	2.60 x 10 ⁻⁵	Additive	1.39 (1.19-1.62)	INTERGENIC
<i>XKR6 - BLK</i>	rs9657519	8	10945439	A	0.56	0.49	5.89 x 10 ⁻⁵	Recessive	1.60 (1.27-2.02)	INTRON (XKR6)
<i>SERGEF</i>	rs2158395	11	17828930	G	0.27	0.35	3.59 x 10 ⁻⁵	Additive	0.70 (0.59-0.83)	INTRON
<i>SERGEF</i>	rs4757590 ^b	11	17822569	C	0.26	0.34	2.23 x 10 ⁻⁵	Additive	0.70 (0.60-0.83)	INTRON
<i>OR9G4-LOC101927120</i>	rs11228824	11	56634316	A	0.24	0.19	6.50 x 10 ⁻⁵	Additive	1.45 (1.21-1.73)	INTERGENIC
<i>SHMT2</i>	rs2229717	12	57627074	T	0.06	0.03	7.98 x 10 ⁻⁵	Dominant	1.99 (1.42-2.81)	SYNONYMOUS CODING
<i>SHMT2</i>	rs28365862 ^b	12	57623363	G	0.07	0.04	3.92 x 10 ⁻⁵	Additive	2.38 (1.58-3.61)	INTERGENIC
<i>RAC2</i>	rs9610687	22	37642869	A	0.25	0.34	4.14 x 10 ⁻⁷	Dominant	0.57 (0.45-0.71)	INTERGENIC

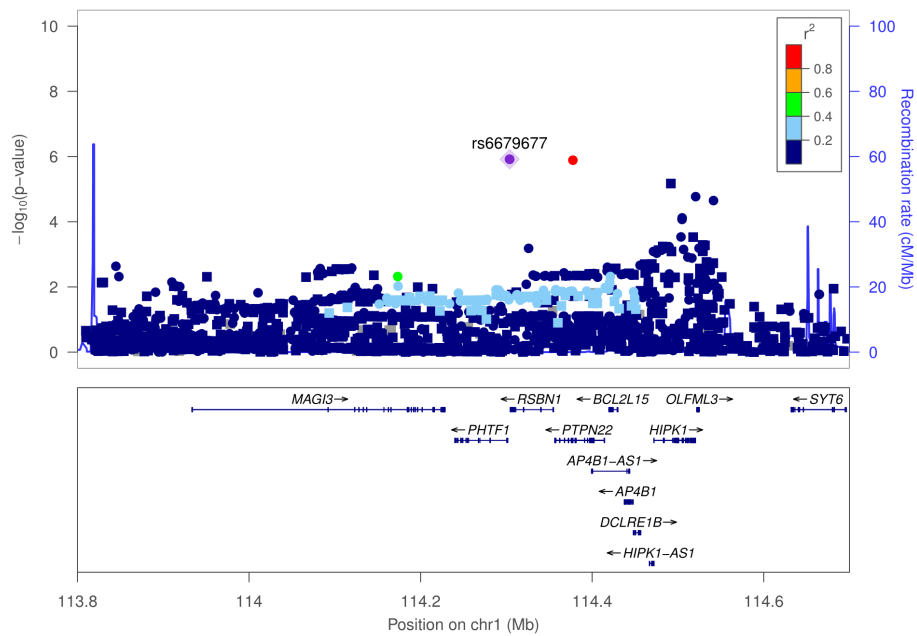
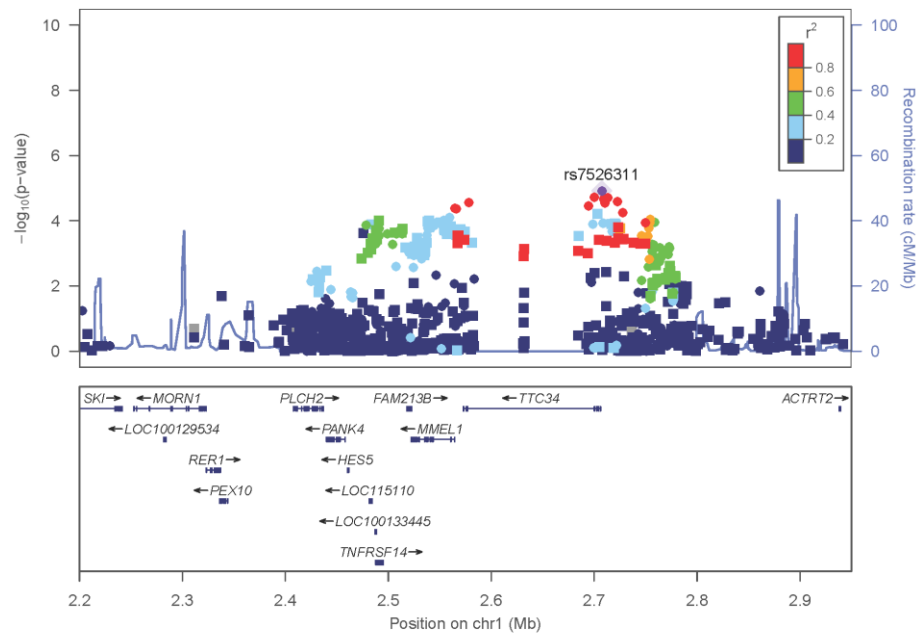
Chr., chromosome; Ref., reference; RAF, reference allele frequency; OR, odds ratio; CI, confidence interval; FDR, false discovery rate.

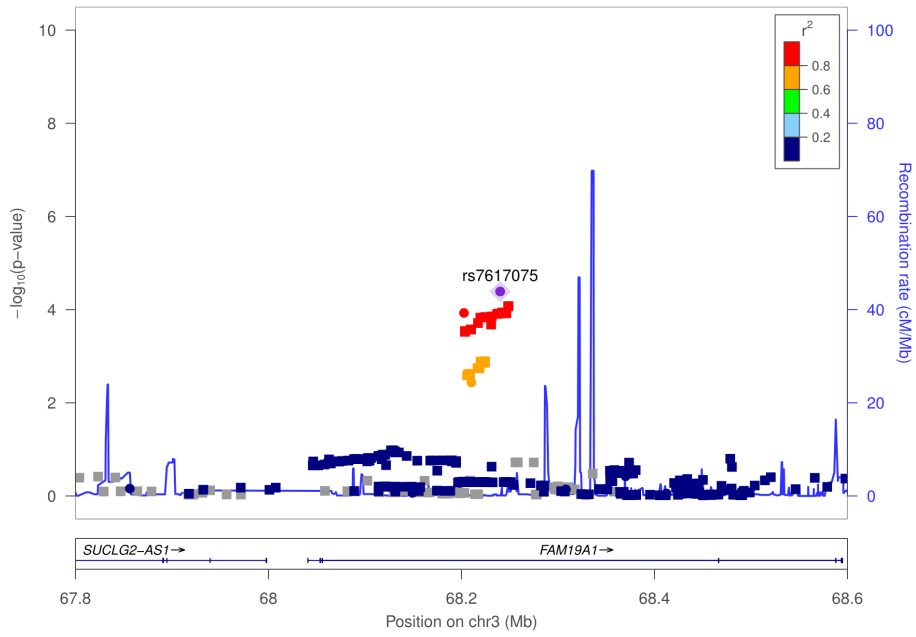
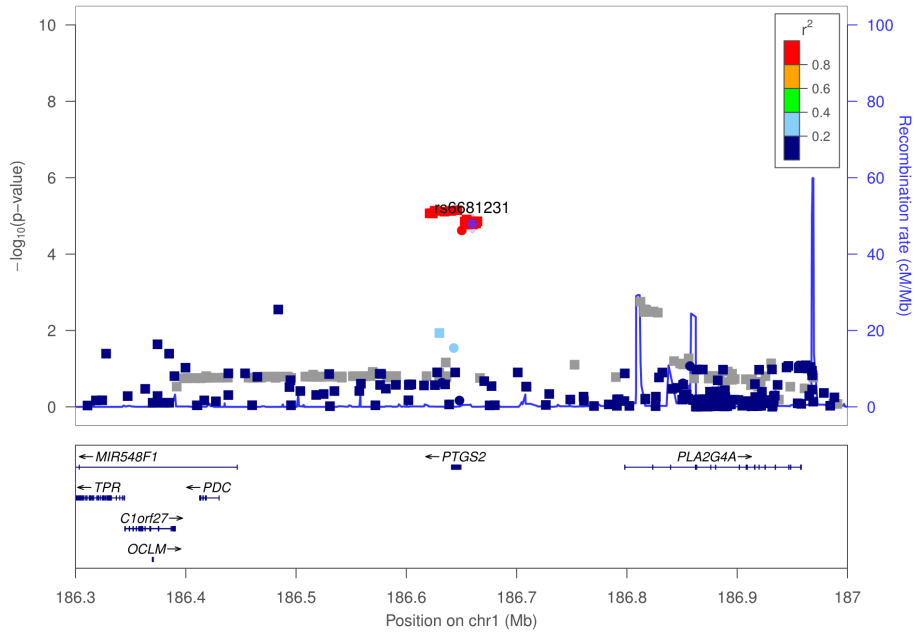
^aCoordinates are based on the GRCh37 assembly. ^bImputed SNP results are included when the imputed ^bSNP had a better imputed *P* value than the most significant directly genotyped SNP in the region.

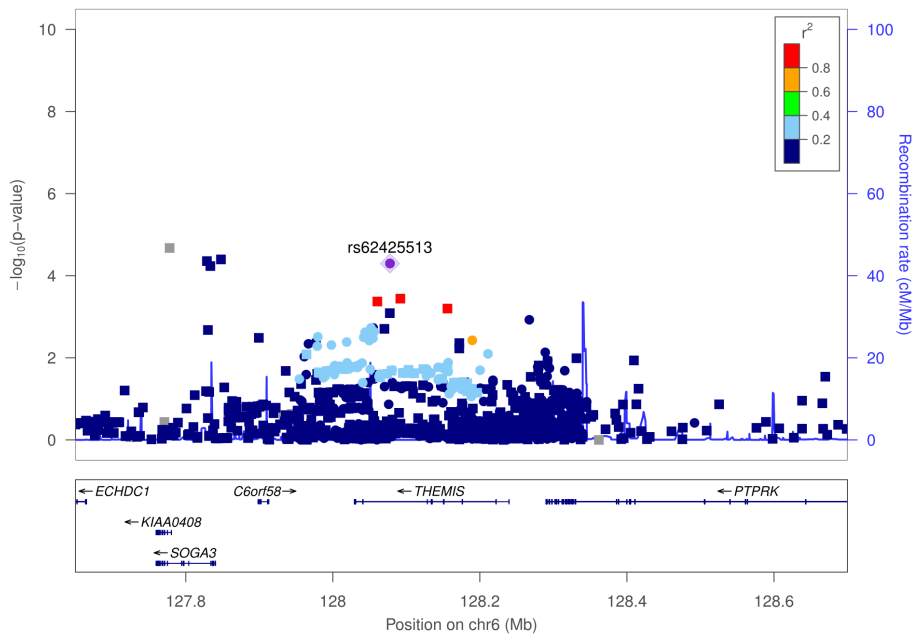
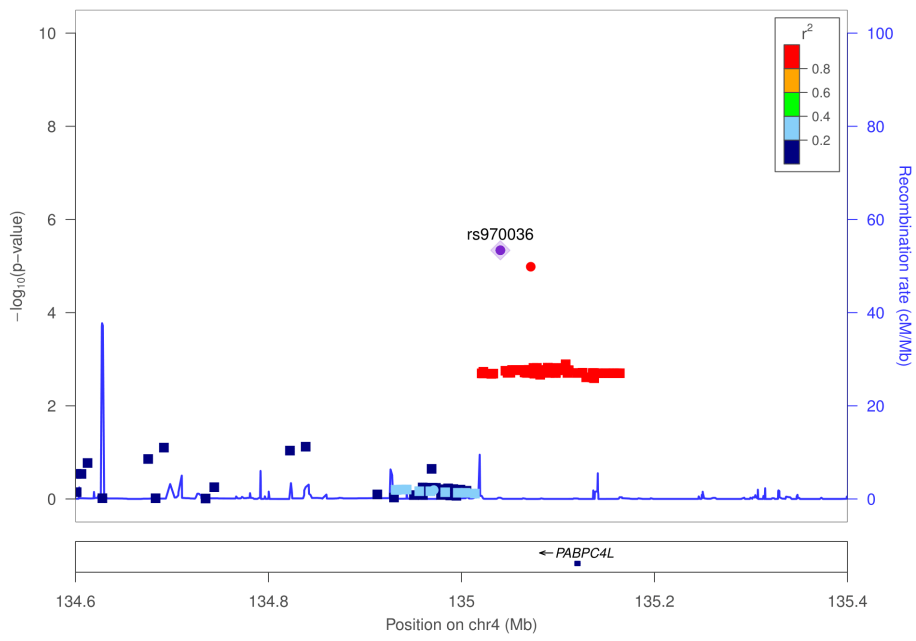
Supplementary Figure 1 Manhattan plot of association statistics for RF-positive polyarticular JIA risk loci

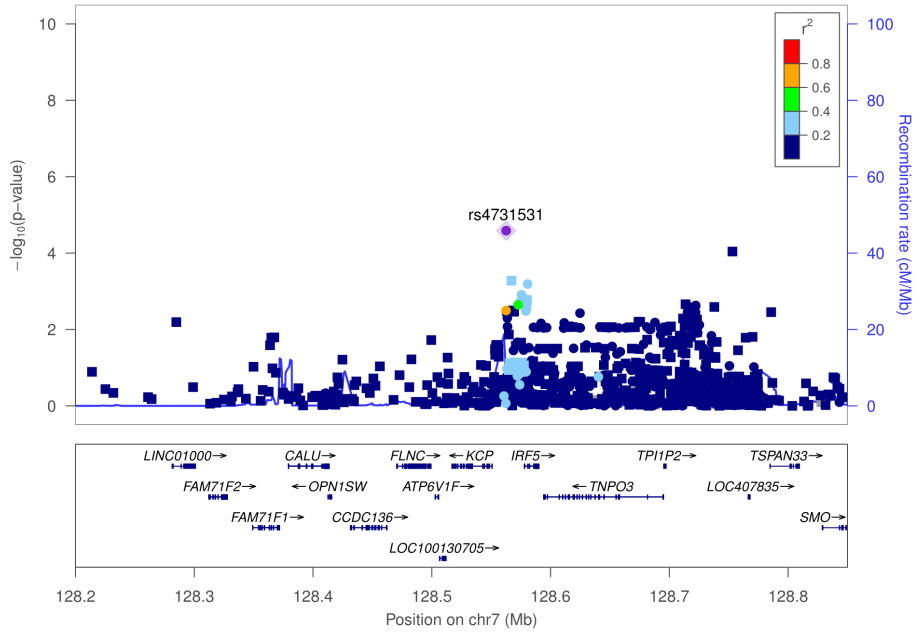
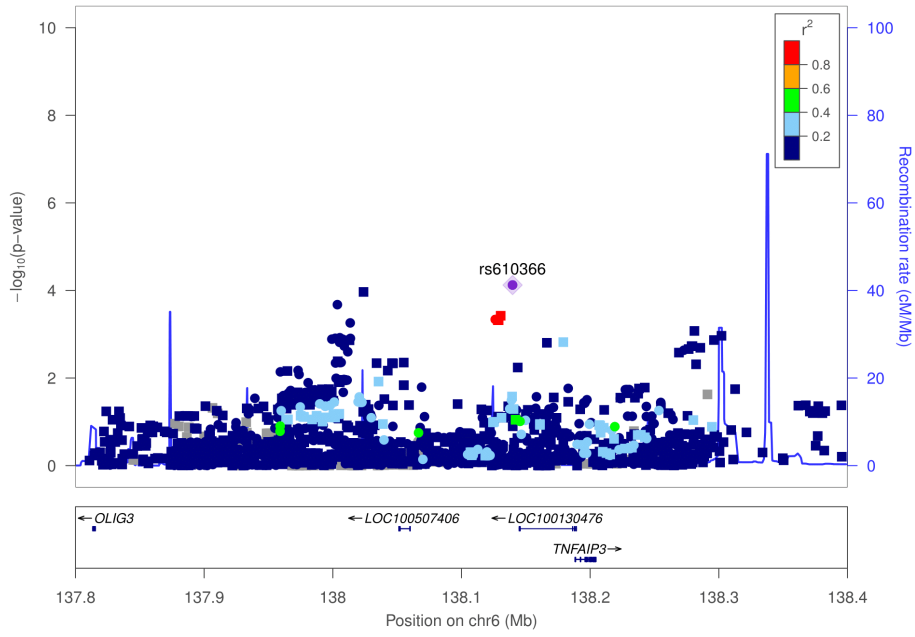


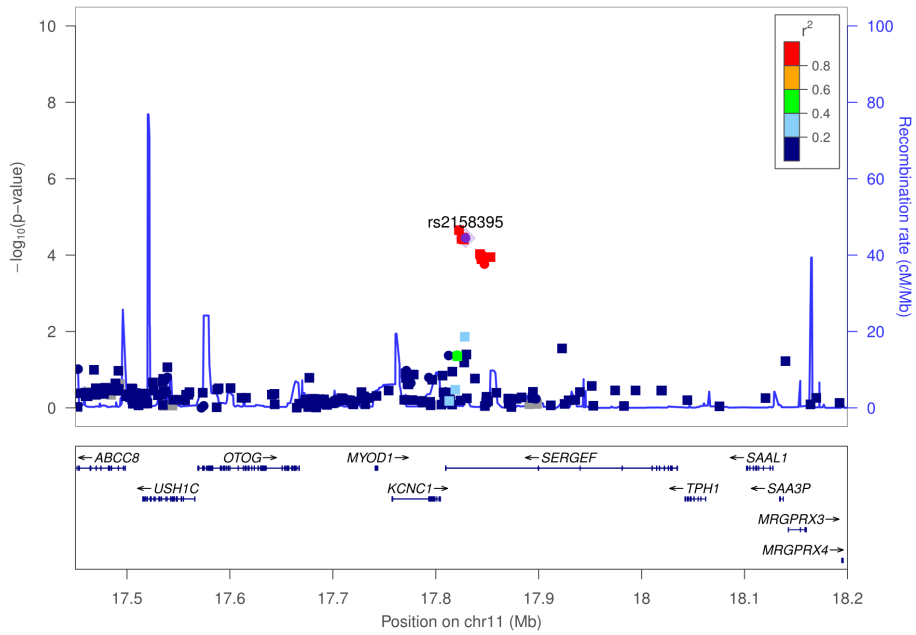
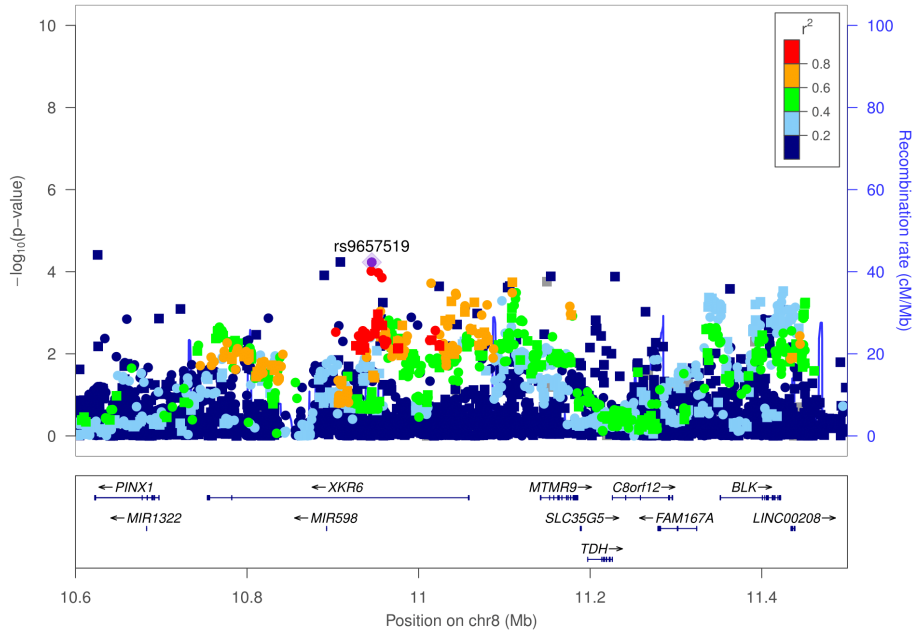
Supplementary Figure 2 Regional association plots for the most significant associations in RF-positive polyarticular JIA

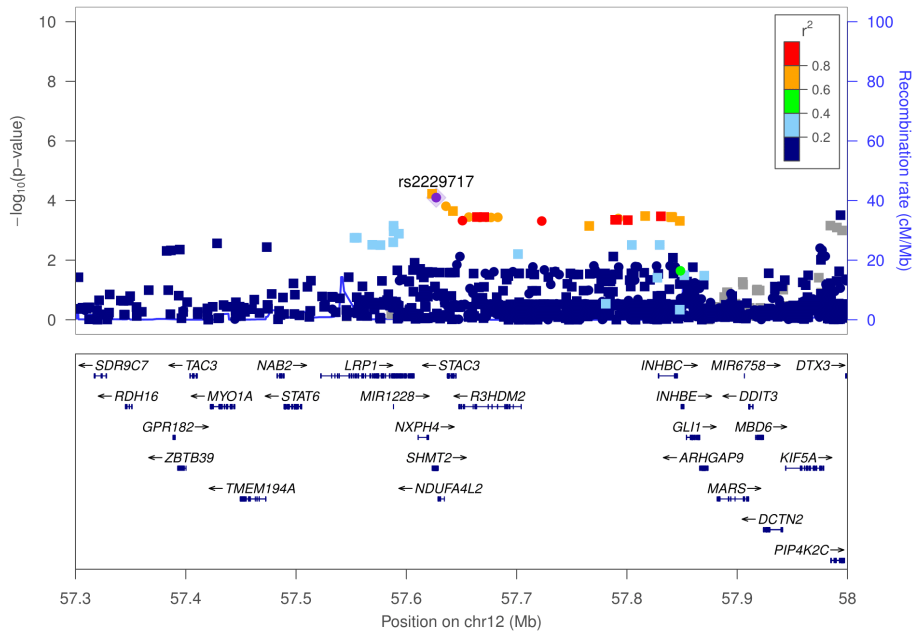
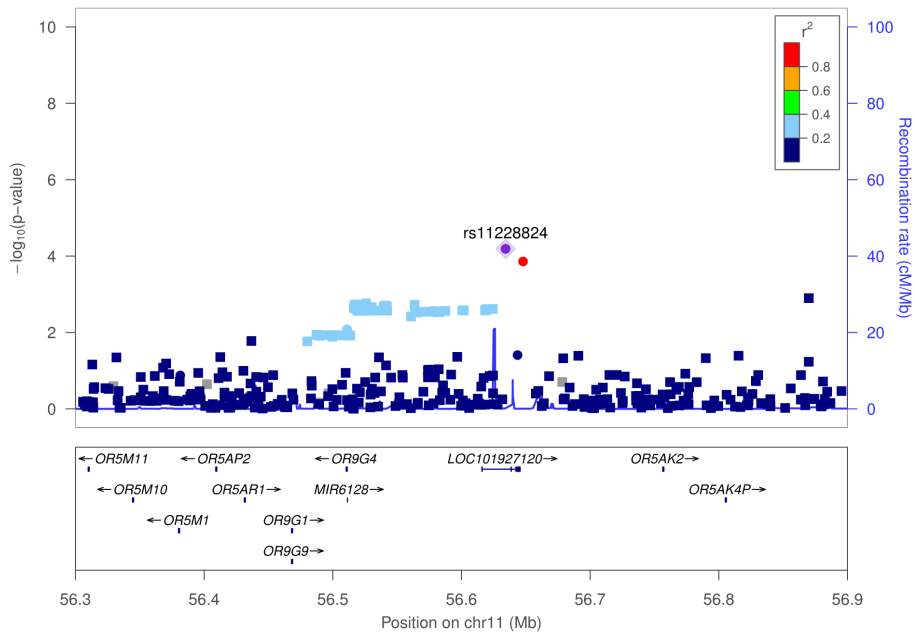


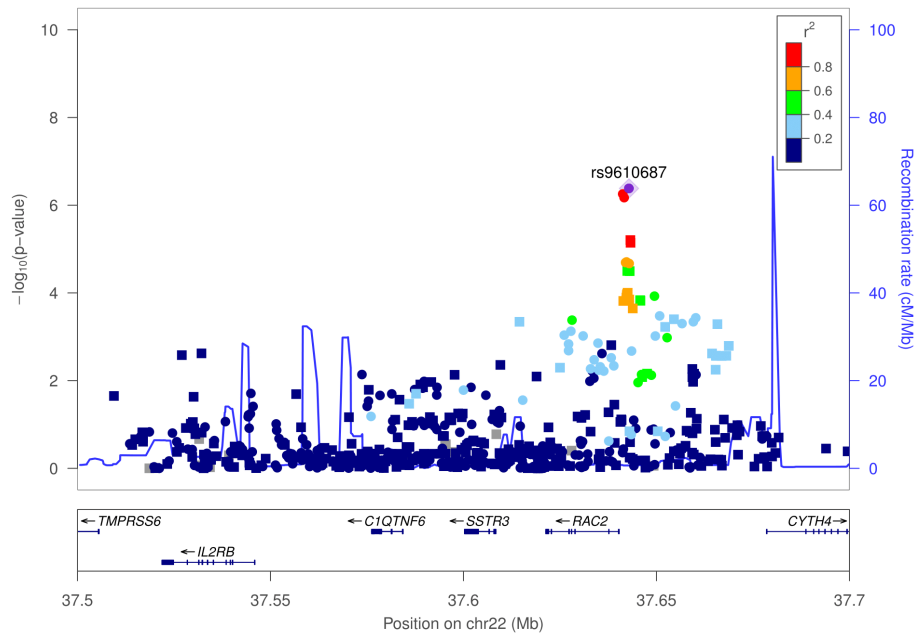












Regional association plots, generated using LocusZoom, for the 13 regions associated with JIA ($P < 1 \times 10^{-4}$) on the left x axis is the $-\log_{10}$ p-value for the SNPs across the region, on the right x axis is the recombination rate across the region and on the y axis is the chromosomal position (Mb). Coordinates are based on the NCBI37 assembly. The SNPs that are genotyped are represented by circles, the SNPs that are imputed by squares. The dots/squares are coloured according to LD (r^2) with the top SNP.

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