SUPPLEMENTARY MATERIAL

Genetic Architecture Distinguishes Systemic Juvenile Idiopathic Arthritis from Other Forms of Juvenile Idiopathic Arthritis: Clinical and Therapeutic Implications

Michael J. Ombrello, Victoria L. Arthur, Elaine F. Remmers, Anne Hinks, Ioanna Tachmazidou, Alexei Grom, Dirk Foell, Alberto Martini, Marco Gattorno, Seza Özen, Sampath Prahalad, Andrew S. Zeft, John F. Bohnsack, Norman T. Ilowite, Elizabeth D. Mellins, Ricardo Russo, Claudio Len, Maria Odete E. Hilario, Sheila Oliveira, Rae S. M. Yeung, Alan Rosenberg, Lucy R. Wedderburn, Jordi Anton, Johannes-Peter Haas, Angela Rosen-Wolff, Kirsten Minden, Klaus Tenbrock, Erkan Demirkaya, Joanna Cobb, Elizabeth Baskin, Sara Signa, Emily Shuldiner, Richard H. Duerr, Jean-Paul Achkar, M. Ilyas Kamboh, Kenneth M. Kaufman, Leah C. Kottyan, Dalila Pinto, Stephen W. Scherer, Marta E. Alarcón-Riquelme, Elisa Docampo, Xavier Estivill, Ahmet Gül, British Society of Pediatric and Adolescent Rheumatology (BSPAR) Study Group, Inception Cohort of Newly Diagnosed Patients with Juvenile Idiopathic Arthritis (ICON-JIA), Childhood Arthritis Prospective Study (CAPS) Group, Randomized Placebo Phase Study of Rilonacept in sJIA (RAPPORT) Investigators, Sparks-Childhood Arthritis Response to Medication Study (CHARMS) Group, Biologically Based Outcome Predictors in JIA (BBOP) Group, Carl D. Langefeld, Susan Thompson, Eleftheria Zeggini, Daniel L. Kastner, Patricia Woo, and Wendy Thomson

FULL ALPHABETICAL MEMBERSHIP LISTING OF COLLABORATING GROUPS

British Society of Pediatric and Adolescent Rheumatology (BSPAR) Study Group:
Mario Abinum[1], A. Bell[2], Alan W. Craft[3], Esther Crawley[4], Joel David[5], Helen Foster[4], Janet Gardener-Medwin[6], Jane Griffin[7], Ann Hall[8], M. Hall[9], Ariane L. Herrick[10], Peter Hollingworth[11], Lennox Holt[12], Stan Jones[13], Gillian Pountain[14], Clive Ryder[15], Tauny Southwood[15], I. Stewart[13], Helen Venning[16], Lucy R. Wedderburn[17], Patricia Woo[4], Sue Wyatt[18]

[1]Department of Immunodeficiency and Paediatric Rheumatology, Newcastle University, Newcastle, U.K.; [2]Queens University, Belfast, U.K.; [3]Royal Victoria Infirmary, Newcastle, U.K.; [4]Division of Infection and Immunity, University College London, London, U.K.; [5]Department of Rheumatology, Nuffield Orthopaedic Hospital, Oxford, U.K.; [6]The Royal Hospital for Sick Children, Yorkhill Children's Hospital, Glasgow, U.K.; [7]Chase Farm Hospital, London, U.K.; [8]Department of Rheumatology, Wexham Park Hospital, Berkshire, U.K.; [9]Department of Rheumatology, Cardiff Royal Infirmary, Cardiff, U.K.; [10]University of Manchester, Manchester Academic Health Science Centre, Salford Royal Hospital, Salford, U.K.; [11]Department of Rheumatology, Bristol Royal Infirmary, Bristol, U.K.; [12]Department of Rheumatology, Manchester University, Manchester, U.K.; [13]Victoria Hospital, Blackpool, Lancashire, U.K.; [14]Hitchingbrooke Hospital, Cambridgeshire, U.K.; [15]Department of Paediatric Rheumatology, Institute of Child Health, Birmingham, Children's Hospital-NHS Foundation Trust, University of Birmingham, Whittall Street, Birmingham, U.K.; [16]Nottingham University Hospital, Nottingham, U.K.; [17]Rheumatology Unit, Institute of Child Health, University College London, London, U.K.; [18]Department of Paediatric Rheumatology, Leeds Children Hospital, Leeds, U.K.

Childhood arthritis prospective study (CAPS) Group:

Eileen Baildam[1], Nick Bishop[2], Lynsey Brown[1], Joanne Buckley[3], Alice Chieng[3], Roberto Carrasco[4], Joanna Cobb[4], Lucy Cook[5], Joyce Davidson[6,7], Annette Duggan[3], Michael Eltringham[5], Helen Foster[5], Elizabeth Friel[7], Mark Friswell[5], Janet Gardner-Medwin[7,8], Paul Gilbert[4], Vikki Gould[6], Kelly Hadfield[4], Kimme Hyrich[4], Julie Jones[9], Sham Lal[4], Mark Lay[4], Gabrielle Lloyd[1], Olivia Lloyd[1], Carol Lydon[1], Natasha Makengo[9], Ann McGovern[3], Alexandra Meijer[9], Nicola Mills-Wierda[7], Theresa Moorcroft[1], Vicki Price[7], Liang Qiao[5], Kay Riding[6], Jane Sim[7], Tauny Southwood[11], Wendy Thomson[4], Maureen Todd[7], Susan Tremble[1], Katharine Venter[1], Debbie Wade[5], Peter Ward[4], Sharon Watson[7], Gwen Webster[1], Lucy R Wedderburn[9, 10], Jadranka Zelenovic[7]

[1]Alder Hey Children's Hospital, Liverpool, U.K.; [2]Academic Unit of Child Health, University of Sheffield, Sheffield, U.K.; [3]The Royal Manchester Children's Hospital, Manchester, U.K.; [4]Arthritis Research UK Epidemiology Unit, Stopford Building, Manchester Academic Health Science Centre, NIHR Manchester Musculoskeletal Biomedical Research Unit, The University of Manchester, Manchester, M13 9PT, U.K.; [5]Royal Victoria Infirmary, Newcastle, U.K.; [6]Royal Hospital for Sick Children, Edinburgh, Scotland, U.K.; [7]Royal Hospital for Sick Children, Yorkhill Children's Hospital, Glasgow, Scotland, U.K.; [8]University of Glasgow, School of Medicine, Glasgow, Scotland, U.K.; [9]Great Ormond Street Hospital, London, U.K.; [10]Rheumatology Unit, UCL Institute of Child Health, London, U.K.; [11]Department of Paediatric Rheumatology, Institute of Child Health, Birmingham Children's Hospital, NHS Foundation Trust, University of Birmingham, Birmingham, U.K.

Randomized Placebo Phase Study of Rilonacept in sJIA (RAPPORT) Investigators:

James D. Birmingham[1], Melissa Elder[2], Beth S. Gottlieb[3], Normal T. Ilowite[4], Lisa F. Imundo[5], Yukiko Kimura[6], Yuliya Lokhnygina[7], Michael L. Miller[8], Diana Milojevic[9], Kathleen O'Neil[10], Marilynn G. Punaro[11], Kristi Prather[7], Natasha M. Ruth[12], Christy I. Sandborg[13], Laura E. Schanberg[14], David D. Sherry[15], Nora G. Singer[16], Steven J. Spalding[17], Stacey E. Tarvin[10], James W. Verbsky[18], Carol A. Wallace[19], and Lawrence S. Zemel[20]

[1]Michigan State University College of Human Medicine, East Lansing, MI; [2]University of Florida, Gainesville, FL; [3]Steven and Alexandra Cohen Children's Hospital, New York, NY; [4]Children's Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, New York [5]Morgan Stanley Children's Hospital of New York-Presbyterian, Columbia University Medical Center, New York, NY; [6]Joseph M. Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack, NJ; [7]Duke Clinical Research Institute, Durham, NC; [8]Ann and Robert H. Lurie Children's Hospital, Chicago, IL; [9]University of California, San Francisco, CA; [10]Riley Hospital for Children, Indianapolis, IN; [11]Texas Scottish Rite Hospital, Dallas, TX; [12]Medical University of South Carolina, Charleston, SC; [13]Stanford University, Stanford, CA; [14]Duke University Medical Center, Durham, NC; [15]Children's Hospital of Philadelphia, PA; [16]Metro Health Medical Center, Cleveland, OH; [17]The Cleveland Clinic, Cleveland, OH; [18]Medical College of Wisconsin, Milwaukee, WI; [16]Seattle Children's Hospital & Research Institute, Seattle, WA; [20]Connecticut Children's Medical Center, Hartford, CT

Sparks-Childhood Arthritis Response to Medication Study (CHARMS) Group:
Kate Armon[1,2], Katrin Burkle[3], Joanna Cobb[4], Rebecca Cutts[5], Angela Etheridge[6], Eirini Giannakopoulou[6], Paul Gilbert[4], Anne Hinks[4], Shashi Hirani[3], Clare Heard[6], Ruth Howman[7], Cerise Johnson[6], Laura Kassoumeri[6], Sham Lal[4], Alice Leahy[5], Lucy Marshall[6], Laura Melville[3], Halima Moncrieffe[6], Kathleen Mulligan[3], Stanton Newman[3], Jason Palman[6], Fiona Patrick[6], Emily Robinson[6], Stephanie Simou[6], Stefanie Stafford[8], Tauny Southwood[7], Wendy Thomson[4], Petra Tucker[2], Simona Ursu[6], Kishore Warrier[8], Joanna Watts[1], Lucy R Wedderburn[6], Pamela Whitworth[7], Patricia Woo[9]

[1]Norfolk & Norwich University Hospital NHF Foundation Trust, Birmingham, U.K.; [2]Cambridge University Hospital NHS Foundation Trust, Cambridge, U.K.; [3]Health Psychology, School of Health Sciences, City University, London, U.K.; [4]Arthritis Research UK Epidemiology Unit, Stopford Building, Manchester Academic Health Science Centre, NIHR Manchester Musculoskeletal Biomedical Research Unit, The University of Manchester, Manchester, U.K.; [5]University Hospital Southampton NHF Foundation Trust, Southampton, U.K.; [6]UCL GOSH Institute of Child Health, London U.K.; [7]Birmingham Children's Hospital NHS Foundation Trust, Birmingham, U.K.; [8]Nottingham University Hospitals NHS Trust, Nottingham, U.K. [9]Division of Infection and Immunity, University College London, London, U.K.

Biologically Based Outcome Predictors in JIA (BBOP) Group:
Adam Baxter-Jones[1], Susanne Benseler[2], Gilles Boire[3], David A. Cabral[4], Bonnie Cameron[2], Sarah Campillo[5], Gaëlle Chedeville[5], Anne-Laure Chetaille[6], Paul Dancey[7], Ciaran Duffy[8], Karen Watanabe Duffy[8], Janet Ellsworth[9], Michele Gibbon[8], Chantal Guillet[10], Jaime Guzman[4], Kristin Houghton[4], Adam M. Huber[11], Roman Jurencak[8], Bianca Lang[11], Ronald M. Laxer[2], Lynn Maenz[1], Loren Matheson[1], Kiem G. Oen[12], Ross E. Petty[4], Suzanne E. Ramsey[11], Elham Rezaei[1], Alan M. Rosenberg[1], Johannes Roth[8], Rayfel Schneider[2], Rosie Scuccimarri[5], Stephen W. Scherer[13], Earl Silverman[2], Lynn Spiegel[2], Elizabeth Stringer[11], Shirley M. L. Tse[2], Lori B. Tucker[4], Stuart Turvey[4], Richard F. Wintle[14] and Rae S. M. Yeung[2]

[1]University of Saskatchewan, Saskatoon, Canada; [2] The University of Toronto and The Hospital for Sick Children, Toronto, Canada; [3]Université de Sherbrooke, Sherbrooke, Canada; [4]British Columbia Children's Hospital, Vancouver, Canada; [5]McGill University, Montreal, Canada; [6]le Centre Hospitalier Universitaire de Quebec, Quebec, Canada; [7]Janeway Children's Health and Rehabilitation Centre, St.John's, Canada; [8]Children's Hospital of Eastern Ontario, Ottawa, Canada; [9]University of Alberta, Edmonton, Canada; [10]Sante et Services Sociaux, Quebec, Canada; [11]IWK Health Centre and Dalhousie University, Halifax, Canada; [12]University of Manitoba, Winnipeg, Canada; [13]The Centre for Applied Genomics, Hospital for Sick Children and McLaughlin Centre and Department of Molecular Genetics, University of Toronto, Toronto, Canada; [14]The Centre for Applied Genomics, Hospital for Sick Children, Toronto, Canada

Inception Cohort of Newly Diagnosed Patients with Juvenile Idiopathic Arthritis (ICON-JIA) Study Group:
Ivan Foeldvari[1], Dirk Foell[2], Gerd Ganser[3], Johannes-Peter Haas[4], Gerd Horneff[5], Anton Hospach[6], Hans-Iko Huppertz[7], Tilmann Kallinich[8], Jasmin Kümmerle-Deschner[9], Kirsten Minden[8], Kirsten Mönkemöller[10], Angela-Roesen Wolff[11], Klaus Tenbrock[12];

Angelika Thon[13]

[1]Hamburg Centre for Pediatric and Adolescent Rheumatology, Hamburg, Germany; [2]University Hospital Münster, Münster, Germany; [3]St. Josef Stift, Seldenhorst, Germany; [4]German Center for Pediatric and Adolescent Rheumatology, Garmisch-Partenkirchen, Germany; [5]Asklepios Clinic Sankt Augustin, Sankt Augustin, Germany; [6]Klinikum Stuttgart Olgahospital, Stuttgart, Germany; [7]Professor Hess Children's Hospital, Bremen, Germany; [8]Charité University Medicine, Berlin, Germany; [9]University of Tübingen Hospital, Tübingen, Germany; [10]Municipal Children's Hospital Köln, Köln, Germany; [11]Children's Hospital Dresden, Dresden, Germany; [12]University Hospital RWTH Aachen, Aachen, Germany; [13]Medical University of Hannover, Children Hospital, Hannover, Germany

PATIENT SAMPLES

Blood samples were obtained from children diagnosed with systemic juvenile idiopathic arthritis (sJIA) by pediatric rheumatologists at collaborating centers in nine countries (Tables 1 and S1). Centralized collections of sJIA patient samples were provided by the British Society for Paediatric and Adolescent Rheumatology's (BSPAR) Juvenile Idiopathic Arthritis Sample Repository at the University of Manchester; the Inception Cohort of Newly Diagnosed Patients with Juvenile Idiopathic Arthritis (ICON-JIA); the Randomized Placebo Phase Study of Rilonacept in the Treatment of Systemic Juvenile Idiopathic Arthritis (RAPPORT); the Childhood Arthritis Prevention Study (CAPS); the Sparks-Childhood Arthritis Response to Medication Study (CHARMS); and the Biologically Based Outcome Predictors in JIA (BBOP). Blood samples from geographically-matched control subjects were obtained, and where available existing SNP genotype data from geographically-matched population control individuals were utilized, *in silico* (Supplementary Table 3). *In silico* control populations included in the study included: 1437 healthy subjects from the University of Pittsburgh and the Cleveland Clinic Foundation with SNP genotypes generated on Illumina Human Omni 1M arrays; 832 healthy subjects from the Cincinnati Children's Hospital Medical Center with SNP genotypes generated on Illumina Human Omni 5M arrays; 1629 population controls from the 1958 British Birth Cohort with SNP genotypes generated on Illumina Human 1M Duo arrays; 2710 population controls from the U.K. National Blood Study with SNP genotypes generated on Illumina Human 1M Duo arrays; 511 healthy subject from the Hospital for Sick Children in Toronto, Canada with SNP genotypes generated with Illumina Human 1M arrays; 260 healthy subjects from Argentina with SNP genotypes generated with Illumina Human Omni 1M arrays; and 200 healthy subjects from Spain with SNP genotypes generated with Illumina HumanHap 300 arrays. Subjects were enrolled into the study in accordance with all local ethics regulations, with approval of each local institutional review board, and with the informed consent of a parent or guardian of each subject.

SNP GENOTYPING AND QUALITY CONTROL OPERATIONS

SNP genotyping of genomic DNA from children with sJIA and healthy children was performed with Human Omni 1M arrays and an iScan bead array reader (Illumina) according to the manufacturer's specifications. SNP genotypes were simultaneously

called for the full set of directly genotyped samples using GenomeStudio software (Illumina) and custom cluster positions generated from the set of directly genotyped samples with the highest call rates. SNPs with GenTrain score < 0.35 (123,541 SNPs) were excluded from further analysis. Samples were stratified by country of origin and affection status, and quality control procedures were performed separately on each group. Samples with call rate < 98% or sample heterozygosity > 3 s.d. from the population-specific mean were excluded from the analysis (Supplementary Table 3). *In silico* SNP genotype data from healthy control subjects were processed using the same quality control parameters, with the exception of the sample call rate, which was determined by analysis of the distribution of call rates within each dataset. Within each stratum, markers were excluded based on the following criteria: MAF < 0.05; SNP call rate < 97%; or Hardy-Weinberg proportion test with $P < 0.0001$ in the population-specific control population. This produced sets of between 156,136 and 740,509 high quality SNPs that were carried forward for subsequent analysis (Supplementary Tables 4).

ASSESSMENT OF POPULATION STRATIFICATION AND ASSEMBLY OF CASE-CONTROL STRATA

To ensure similarity of continental ancestry among the membership of each group of cases or controls, we merged the data from each sample group with SNP genotype data from the European (CEU and TSI), African (ASW, YRI), Asian (CHB, JPT), and Hispanic and South Asian (MEX and GIH) HapMap3 populations. Each dataset was pruned on the basis of pairwise linkage disequilibrium (LD), removing one member of each pair of SNPs with $r^2 < 0.4$ using the estimation-maximization (EM) method. We also excluded the 24 regions of long-range LD identified by Price *et al*[1]. The LD-reduced datasets were subjected to multidimensional scaling analysis (MDS) with PLINK v1.07[2]. Outliers of continental ancestry were identified and excluded from each group by visual inspection of MDS plots. Principal components analysis (PCA) was subsequently performed on the LD-reduced SNP set from each group to more stringently identify and remove genetic outliers, thereby restricting the ancestral membership of the groups. In the U.S. case stratum, the datasets from the five contributing centers were consolidated into a single stratum, retaining only the intersecting set of SNPs from the five groups. Pairwise comparisons of allelic frequencies were performed between the five groups to and SNPs whose frequencies differed significantly ($p < 5 \times 10^{-8}$) between any pair of U.S. sJIA groups were excluded. PCA was repeated on the full U.S. case stratum to insure common ancestry across the five groups. Geographically-matched case and control groups were each combined to form the nine case-control strata, each composed of the SNP intersection between the respective case and control groups. Finally, PCA was performed on LD-reduced SNP sets from each case-control stratum to identify and exclude ancestrally dissimilar individuals. Genomic control inflation factors were also calculated using the LD-reduced sets of SNPs from each case-control stratum to objectively quantify their ancestral composition. The sample quality control process produced nine case-control strata with a total of 770 sJIA cases and 6947 control subjects that were subsequently analyzed (Table 1, Supplementary Table 3).

SNP IMPUTATION, ASSOCIATION TESTING, AND META-ANALYSIS OF THE MHC LOCUS

Using the high-quality sets of directly genotyped SNPs, we performed genome-wide SNP imputation separately in each separately in each of the nine case-control strata. Genotypes were phased using the Markov Chain Monte Carlo algorithm implemented in IMPUTE2 v2.3.2[3] software. SNP imputation was performed using IMPUTE2 v2.3.2 and a multi-ethnic reference panel of phased haplotypes from the 1000Genomes project (Phase3 integrated dataset), as previously described[4]. Following SNP imputation, genotypic probabilities from the set of common SNPs (MAF > 0.04 in case collections) that were imputed with high quality (info > 0.8) were subjected to frequentist association testing with SNPTESTv2.5 software under the additive and dominant models, adjusting for gender and ancestry informative principal components. Association meta-analyses were performed using GWAMA[5] software under the fixed-effect model. Heterogeneity of effect was evaluated in using the I^2 statistic and markers with a high probability of heterogeneity ($I^2 > 0.7$) were excluded. The meta-analytic associations of the set of SNPs with ORs between 0.25 and four that were evaluated in 4 or more strata and a minimum of 2500 samples were included in subsequent analyses.

COMPARISON OF GENETIC ARCHITECTURE OF SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS WITH THOSE OF OLIGOARTICULAR AND POLYARTICULAR FORMS OF JUVENILE IDIOPATHIC ARTHRITIS

To compare the genetic architecture of sJIA with those of oligoarticular and seronegative polyarticular juvenile idiopathic arthritis (JIA), we analyzed weighted genetic risk scores (wGRS) according to the method of Karlson and colleagues[6]. wGRS were calculated in each individual as the sum of the risk allele counts, weighted by the natural logarithm of the odds ratio (OR). For the group of oligoarticular and seropositive polyarticular JIA (polygoJIA), the wGRS incorporated 23 independent polygoJIA risk SNPs reported by Hinks and colleagues[7]. For rheumatoid factor positive polyarticular JIA (RF+polyJIA), we utilized the wGRS-11 that was previously reported by Prahalad and colleagues[8]. For each wGRS, scatter plots and kernel density plots were generated to visually compare the wGRS distributions between the cases and controls in each stratum and in the full collection. The case and control distributions of risk alleles and wGRSs were evaluated with the non-parametric Wilcoxon Rank Sum Test. Association of wGRSs with sJIA was also tested in each individual stratum and in the full study collection using logistic regression, adjusted for gender and ancestry. Furthermore, receiver operator characteristic (ROC) curves were generated and the area under the curve (AUC) calculation was performed using R in each of the 9 strata and in the full study population to determine the ability of the wGRSs to discriminate between sJIA and other JIA subtypes. In to wGRS analyses, the genetic architecture of sJIA was compared with that of polygoJIA using conditional quantile-quantile (Q-Q) plots, as previously reported [9]. Specifically, we generated a Q-Q plot of meta-analytic association with sJIA for all SNPs that were also examined in the study of polygoJIA by Hinks and colleagues[7]. We also created Q-Q plots for five sets of SNPs with increasing levels of association with polygoJIA: p < 0.1; p < 0.01; p < 0.001; p < 0.0001; and p < 0.00001.

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Table S1. Variables included in the polygo JIA weighted genetic risk score (polygo-wGRS)

Gene/Locus	Marker	Polygo JIA Risk Allele
HLA-DQB1-HLA-DQA2	rs7775055	G
PTPN22	rs6679677	A
STAT4	rs10174238	G
PTPN2	rs2847293	A
ANKRD55	rs71624119	G
ANKRD55	rs10213692	T
IL2-IL2I	rs1479924	A
IL2RA	rs7909519	A
SH2B3-ATXN2	rs3184504	A
SH2B3-ATXN2	rs7137828	C
ERAP2-LNPEP	rs27290	G
ERAP2-LNPEP	rs27293	A
UBE2L3	rs2266959	A
C5orf56-IRF1	rs6894249	A
C5orf56-IRF1	rs4705862	A
RUNX1	rs8129030	A
RUNX1	rs9979383	A
IL2RB	rs2284033	G
ATP8B2-IL6R	rs11265608	A
ATP8B2-IL6R	rs72698115	C
FAS	rs7069750	C
ZFP36L1	rs12434551	T
ZFP36L1	rs3825568	C

Polygo, rheumatoid factor negative polyarticular and oligoarticular juvenile idiopathic arthritis. wGRS, weighted genetic risk scores. sJIA, systemic juvenile idiopathic arthritis.

Table S2. Variables included in the rheumatoid factor positive polyarticular JIA weighted genetic risk score (wGRS-11) from Prahalad et al.[a]

Gene	Marker	RF+ Poly JIA Risk Allele
HLA-DRB1	HLA-DRB1*0101	Present
HLA-DRB1	HLA-DRB1*0401	Present
HLA-DRB1	HLA-DRB1*0404	Present
HLA-DRB1	HLA-DRB1*0405	Present
HLA-DRB1	HLA-DRB1*1001	Present
HLA-DRB1	HLA-DRB1*0901	Present
PTPN22	rs2476601	T
STAT4	rs7574865	T
TNFAIP3	rs10499194	T
TNFAIP3	rs6920220	A
TRAF-C5	rs3761847	G

[a] In the report by Prahalad et al.[18], the wGRS-11 was significantly associated with rheumatoid factor positive polyarticular JIA (odds ratio = 3.32; $p < 2 \times 10^{-16}$).

Table S3. Summary of sample quality control procedures

Stratum	Population	Samples	EXCLUSION CRITERIA					Excluded	Included
			Heterozygosity	Call Rate	Relatedness	MDS	PCA		
U.S.	Cincinnati sJIA	225	14	0	8	41	10	64	161
	Stanford sJIA	34	0	0	0	19	2	21	13
	Utah sJIA	42	2	0	0	8	4	10	32
	Emory sJIA	20	0	0	0	6	1	7	13
	RAPPORT sJIA	40	0	0	1	13	2	16	24
U.K.	U.K. sJIA	228	6	12	0	10	4	26	202
Germany	Germany sJIA	159	4	0	11	17	14	44	115
	Germany controls	209	0	0	11	4	3	16	193
Turkey	Turkey sJIA	54	3	0	1	0	1	5	49
	Turkey controls	96	0	2	0	0	0	2	94
Italy	Italy sJIA	55	2	3	1	2	0	6	49
	Italy controls	60	1	0	0	0	0	1	59
Brazil	Brazil sJIA	51	1	0	0	2	0	3	48
	Brazil controls	66	1	0	1	2	0	4	62
Argentina	Argentina sJIA	33	0	0	0	0	0	0	33
Canada	Canada sJIA	25	0	0	0	8	0	8	17
Spain	Spain sJIA	16	1	1	0	0	0	2	14
Total (sJIA/controls)		**982/431**	**33/2**	**16/2**	**22/12**	**126/6**	**38/3**	**212/23**	**770/408**

Directly Genotyped Samples

Stratum	Population	Samples	Heterozygosity	Call Rate	Relatedness	MDS	PCA	Excluded	Included
U.S.	Pitt/CCF Controls	1437	21	61	0	0	438	511	926
	Cincinnati Controls	832	33	0	0	0	7	40	792
U.K.	1958BC Controls	1629	8	11	19	0	14	33	1596
	NBS Controls	2710	111	0	48	0	51	209	2501
Spain	Spain Controls	200	5	4	9	0	0	18	182
Argentina	Argentina Controls	260	6	47	16	0	132	145	115
Canada	Canada Controls	511	6	36	36	0	45	84	427
Total *in silico* controls		**7579**	**191**	**159**	**128**	**0**	**641**	**1040**	**6539**

In Silico Samples

sJIA, systemic juvenile idiopathic arthritis. Pitt, University of Pittsburgh. CCF, Cleveland Clinic Foundation. 1958BC, U.K.1958 British Birth Cohort. NBS, U.K. National Blood Service Study. MDS, multidimensional scaling. PCA, principal components analysis. From Ombrello MJ *et al. Proc Natl Acad Sci U S A* 2015; 112(52): 15970-5.

Table S4. Summary of SNP quality control procedures

Stratum	Population	SNPs	EXCLUSION CRITERIA MAF < 5%	Non-Autosomal	Call Rate	HWE	Excluded	Remaining	Intersecting directly genotyped SNPs	Imputed SNPs	Imputed SNPs (post-QC)
U.S.	Merged U.S. sJIA	1,062,530	445,457		2448		447,905	614,625	476,196	18,263,974	6,189,397
	Cincinnati Controls*	4,292,363	2,555,243	18,823	52,643	120,073	2,620,221	1,672,142			
	Pitt/CCF Controls*	1,053,035	334,026		18,839	2550	363,570	698,960			
U.K.	U.K. sJIA	1,062,530	347,154		23,363		370,517	692,013	440,688	18,263,701	6,255,387
	1958BC Controls*	914,714	86,149		0	2991	89,140	825,574			
	NBS Controls*	1,115,428	178,713	1537	20,224	14,374	214,848	900,580			
Germany	Germany sJIA	1,062,530	349,606		6,974		356,580	705,950	682,516	18,266,121	6,391,432
	Germany Controls	1,062,530	349,193		14,537	760	363,991	698,539			
Turkey	Turkey sJIA	1,062,530	332,343		4744		337,087	725,443	682,598	18,270,612	6,389,103
	Turkey Controls	1,062,530	337,395		22,045	560	359,667	702,863			
Italy	Italy sJIA	1,062,530	340,450		9930		350,380	712,150	686,397	18,269,173	6,375,260
	Italy Controls	1,062,530	340,986		3756	388	344,919	717,611			
Brazil	Brazil sJIA	1,062,530	277,488		3174		280,662	781,868	740,509	18,263,563	6,698,947
	Brazil Controls	1,062,530	288,033		7968	430	296,197	766,333			
Argentina	Argentina sJIA	1,062,530	347,035		20,552		367,587	694,943	659,100	18,263,401	6,129,601
	Argentina Controls*	985,839	272,864		68,333	482	273,105	712,734			
Canada	Canada sJIA	1,062,530	357,390		29,262		386,652	675,878	396,935	18,263,146	5,812,530
	Canada Controls*	1,027,449	242,748	22,510	26,109	3636	270,675	736,311			
Spain	Spain sJIA	1,062,530	375,042		38,205		413,247	649,283	156,136	18,261,199	4,147,550
	Spain Controls*	311,273	10,432	8350	5078	3512	17,266	287,593			

* *in silico* control populations**.** SNP, single nucleotide polymorphism. MAF, minor allele frequency. HWE, Hardy Weinberg equilibrium. QC, quality control. modified from Ombrello MJ *et al. Proc Natl Acad Sci U S A* 2015; 112(52): 15970-5.

Table S5. Examination of peak SNPs from polygoJIA susceptibility loci in sJIA case-control collections[*]

PolygoJIA risk locus[a]	PolygoJIA peakSNP	PolygoJIA p-value	PolygoJIA OR (95 C.I.)	sJIA p-value[b,c]	sJIA OR (95 C.I.)	i^2	N studies/ N samples
HLA-DQB1-HLA-DQA2	rs7775055	3.1×10^{-174}	6.0 (5.3, 6.8)	0.3	1.5 (0.7, 2.8)	0	3/399
PTPN22	rs6679677	1.4×10^{-12}	1.6 (1.5, 1.7)	0.1	1.2 (1.0, 1.5)	0	6/7314
STAT4	rs10174238	1.3×10^{-13}	1.3 (1.2, 1.4)	0.2	1.2 (0.9, 1.6)	0.46	3/559
PTPN2	rs2847293	1.4×10^{-12}	1.3 (1.2, 1.4)	0.1	0.7 (0.4, 1.2)	0.25	7/7408
ANKRD55	rs71624119	4.4×10^{-11}	0.8 (0.7, 0.8)	2.8×10^{-3}	0.7 (0.6, 0.9)	0.10	4/2517
	rs10213692	2.7×10^{-11}	0.8 (0.7, 0.8)	2.9×10^{-3}	0.7 (0.6, 0.9)	0.16	4/2516
IL2-IL2I	rs1479924	6.2×10^{-11}	0.8 (0.7, 0.9)	0.5	1.1 (0.8, 1.5)	0	9/7713
IL2RA	rs7909519	8.0×10^{-10}	0.7 (0.6, 0.8)	0.2	0.9 (0.7, 1.1)	0.57	9/7711
SH2B3-ATXN2	rs3184504	2.6×10^{-9}	1.2 (1.1, 1.3)	0.09	1.1 (1.0, 1.2)	0	9/7714
	rs7137828	1.6×10^{-9}	1.2 (1.1, 1.3)	0.1	1.1 (1.0, 1.2)	0	9/7708
ERAP2-LNPEP	rs27290	7.5×10^{-9}	1.3 (1.2, 1.5)	0.06	1.2 (1.0, 1.5)	0	9/7713
	rs27293	7.4×10^{-9}	1.3 (1.2, 1.4)	0.06	1.2 (1.0, 1.5)	0	9/7712
UBE2L3	rs2266959	6.2×10^{-9}	1.2 (1.2, 1.3)	0.3	1.1 (0.9, 1.3)	0	9/7713
C5orf56-IRF1	rs6894249	9.7×10^{-10}	0.8 (0.7, 0.8)	0.5	1.1 (0.9, 1.3)	0	9/7711
	rs4705862	1.0×10^{-8}	0.8 (0.8, 0.9)	0.5	1.0 (0.9, 1.1)	0	8/7513
RUNX1	rs8129030	5.4×10^{-9}	0.8 (0.7, 0.8)	0.7	1.0 (0.9, 1.1)	0	8/7513
	rs9979383	1.1×10^{-8}	0.8 (0.7, 0.9)	0.9	1.0 (0.9, 1.1)	0	8/7520
IL2RB	rs2284033	1.6×10^{-8}	0.8 (0.8, 0.9)	0.5	1.0 (0.9, 1.2)	0	9/7716
ATP8B2-IL6R	rs11265608	2.8×10^{-8}	1.3 (1.2, 1.5)	0.03	1.3 (1.0, 1.6)	0	6/7229
	rs72698115	1.3×10^{-8}	1.4 (1.2, 1.5)	0.05	1.3 (1.0, 1.6)	0	6/7226
FAS	rs7069750	2.9×10^{-8}	1.2 (1.1, 1.3)	0.6	1.0 (0.9, 1.2)	0	9/7712
ZFP36L1	rs12434551	1.6×10^{-8}	0.8 (0.7, 0.9)	0.5	1.0 (0.9, 1.1)	0.38	9/7711
	rs3825568	1.2×10^{-8}	0.8 (0.7, 0.8)	0.8	1.0 (0.9, 1.1)	0.43	9/7712

[*] TYK2 variant was not examined because its frequency was below the quality control thresholds of the present study. [a] Peak polygoJIA-associated SNPs as reported by Hinks et al.[11]. [b] Association testing was performed under the same model reported by Hinks et al.[11]. [c] Significance threshold is p < 0.0022 (0.05 / 23 independent SNPs tested). SNP, single nucleotide polymorphism. polygoJIA, rheumatoid factor negative polyarticular and oligoarticular juvenile idiopathic arthritis. OR, odds ratio for the minor allele. 95 C.I., 95% confidence interval of the odds ratio. sJIA, systemic juvenile idiopathic arthritis. I^2, I^2 test of heterogeneity. N studies, number of strata included in meta-analysis. N samples, number of samples (cases + controls) included in meta-analysis.

Table S6. Minor allele frequencies of polygoJIA risk SNPs in from polygoJIA ImmunoChip study and from INCHARGE sJIA case and control collections.

Polygo risk SNP	Hinks et al.		U.K.		U.S.		Germany		Italy		Turkey		Brazil		Argentina		Canada		Spain	
	Polygo	HC	sJIA	HC	sJIA	HC	sJIA	HC	sJIA	HC	sJIA	HC	sJIA	HC	sJIA	HC	sJIA	HC	sJIA	HC
rs7775055	0.12	0.02	0.03	0.02	0.04	0.03	0.04	0.03	0.01	0.03	0.05	0.02	0.07	0.07	0.12	0.09	0.00	0.02	0.04	0.02
rs6679677	0.14	0.10	0.10	0.10	0.10	0.08	0.13	0.10	0.06	0.04	0.03	0.04	0.01	0.03	0.03	0.04	0.15	0.10	0.10	0.07
rs10174238	0.28	0.23	0.24	0.24	0.24	0.26	0.25	0.20	0.30	0.19	0.26	0.30	0.33	0.32	0.29	0.39	0.36	0.25	0.44	0.23
rs2847293	0.20	0.17	0.13	0.16	0.15	0.16	0.11	0.13	0.16	0.11	0.18	0.09	0.17	0.19	0.12	0.12	0.15	0.15	0.04	0.16
rs71624119	0.20	0.25	0.20	0.23	0.18	0.23	0.23	0.28	0.23	0.19	0.19	0.25	0.16	0.19	0.13	0.16	0.23	0.22	0.15	0.23
rs10213692	0.20	0.25	0.20	0.24	0.18	0.23	0.23	0.28	0.23	0.19	0.18	0.25	0.17	0.20	0.13	0.16	0.24	0.22	0.15	0.23
rs1479924	0.24	0.29	0.25	0.29	0.29	0.28	0.28	0.24	0.35	0.32	0.24	0.23	0.28	0.26	0.21	0.19	0.09	0.27	0.32	0.32
rs7909519	0.08	0.11	0.07	0.11	0.12	0.10	0.09	0.12	0.06	0.07	0.13	0.08	0.06	0.09	0.06	0.05	0.09	0.10	0.19	0.08
rs3184504	0.54	0.49	0.51	0.48	0.53	0.49	0.48	0.47	0.50	0.45	0.40	0.36	0.37	0.38	0.36	0.34	0.59	0.49	0.36	0.44
rs7137828	0.54	0.49	0.50	0.48	0.53	0.49	0.49	0.47	0.49	0.45	0.39	0.36	0.36	0.38	0.36	0.36	0.58	0.49	0.36	0.44
rs27290	0.47	0.44	0.43	0.45	0.42	0.45	0.40	0.46	0.35	0.41	0.33	0.26	0.34	0.29	0.29	0.32	0.50	0.44	0.31	0.40
rs27293	0.47	0.44	0.43	0.45	0.42	0.45	0.40	0.46	0.35	0.41	0.33	0.26	0.34	0.29	0.29	0.32	0.50	0.44	0.31	0.40
rs2266959	0.22	0.19	0.21	0.19	0.19	0.19	0.17	0.21	0.25	0.17	0.27	0.18	0.23	0.24	0.38	0.30	0.21	0.18	0.25	0.17
rs6894249	0.35	0.39	0.37	0.39	0.38	0.38	0.40	0.40	0.37	0.27	0.44	0.38	0.48	0.50	0.52	0.47	0.27	0.35	0.37	0.37
rs4705862	0.39	0.44	0.42	0.44	0.42	0.43	0.44	0.45	0.46	0.36	0.45	0.50	0.44	0.44	0.48	0.49	0.31	0.41	0.45	0.42
rs8129030	0.33	0.37	0.38	0.37	0.37	0.37	0.33	0.37	0.31	0.39	0.30	0.35	0.23	0.27	0.33	0.34	0.41	0.33	0.28	0.36
rs9979383	0.33	0.37	0.39	0.37	0.38	0.37	0.33	0.37	0.32	0.41	0.31	0.37	0.23	0.26	0.35	0.34	0.41	0.34	0.27	0.37
rs2284033	0.39	0.44	0.45	0.44	0.41	0.42	0.44	0.39	0.36	0.42	0.36	0.41	0.35	0.32	0.45	0.33	0.44	0.40	0.43	0.40
rs11265608	0.12	0.10	0.11	0.10	0.12	0.09	0.15	0.13	0.04	0.04	0.03	0.02	0.11	0.05	0.03	0.05	0.06	0.10	0.00	0.08
rs72698115	0.12	0.10	0.11	0.10	0.12	0.09	0.15	0.12	0.04	0.04	0.03	0.02	0.05	0.05	0.02	0.05	0.05	0.10	0.00	0.08
rs7069750	0.48	0.44	0.45	0.44	0.47	0.45	0.43	0.42	0.46	0.47	0.39	0.44	0.48	0.48	0.49	0.45	0.46	0.46	0.37	0.45
rs12434551	0.43	0.47	0.46	0.47	0.44	0.47	0.47	0.45	0.48	0.36	0.38	0.55	0.50	0.40	0.49	0.44	0.41	0.43	0.43	0.49
rs3825568	0.42	0.46	0.46	0.47	0.45	0.47	0.47	0.45	0.49	0.36	0.38	0.55	0.48	0.38	0.48	0.45	0.41	0.44	0.44	0.49

PolygoJIA, rheumatoid factor negative polyarticular and oligoarticular juvenile idiopathic arthritis. SNP, single nucleotide polymorphism. sJIA, systemic juvenile idiopathic arthritis. HC, healthy control subject.

Table S7. Evaluation of polygo-wGRS in sJIA case-control collections

Stratum	Wilcoxon Rank Sum Test p-value		Polygo-wGRS Logistic Regression p-value
	Polygo-wGRS	Polygo Risk Alleles	
Full collection	0.065	0.112	0.261
Argentina	0.761	0.394	0.479
Brazil	0.945	0.494	0.967
Canada	0.720	0.134	0.799
Germany	0.732	0.558	0.696
Italy	0.926	0.939	0.819
Spain	0.546	0.828	0.944
Turkey	0.415	0.080	0.491
U.K.	0.173	0.103	0.450
U.S.	0.497	0.350	0.462

Polygo, rheumatoid factor negative polyarticular and oligoarticular juvenile idiopathic arthritis. wGRS, weighted genetic risk scores. sJIA, systemic juvenile idiopathic arthritis.

Table S8. Evaluation of RF+poly-wGRS in sJIA case-control collections

Stratum	Wilcoxon Rank Sum Test p-value		RF+Poly-wGRS Logistic Regression p-value
	RF+Poly wGRS	RF+Poly Risk Alleles	
Full collection	0.006	0.747	0.0151
Argentina	0.732	1.0	0.894
Brazil	0.508	0.479	0.388
Canada	0.522	0.836	0.341
Germany	0.798	0.889	0.992
Italy	0.777	0.862	0.732
Spain	0.435	0.693	0.154
Turkey	0.643	0.397	0.906
U.K.	0.197	0.563	0.398
U.S.	0.283	0.841	0.452

RF+poly, rheumatoid factor positive polyarticular juvenile idiopathic arthritis. wGRS, weighted genetic risk score. sJIA, systemic juvenile idiopathic arthritis.

Table S9. Reported associations (p < 1 x 10^{-5}) between suggestive sJIA susceptibility loci and other diseases.

	Polygenic diseases	Monogenic diseases
COL11A1	*Primary angle closure glaucoma* Lumbar degenerative disc disease	Stickler syndrome Skeletal dysplasia
HDAC9	*Stroke* *Coronary artery disease* Peripheral artery disease Ulcerative colitis Non-diabetic retinopathy	
LOC101929446	Obsessive-compulsive disorder Inflammatory skin disease Amyotrophic lateral sclerosis	
PRICKLE2	*Type 2 diabetes* Coronary artery calcification	
ZNF521	Schizophrenia Periodontitis	
EIF3H	*Colorectal cancer* *Ossification of posterior longitudinal ligament of spine*	
WWOX	Type 2 diabetes	Spinocerebellar atrophy Infantile epileptic epilepsy
LOC101928737 / JPH3	Schizophrenia Major depressive disorder Bipolar disorder Alzheimer's disease	
LOC101927573 / SORCS1	Endometriosis Prion disease	
TRIM58	Spontaneous pituitary adenoma	
LOC101928516 / COL12A1		Congenital myopathy
LOC257396 / MOCS2	*Acne* Schizophrenia	Molybdenum cofactor deficiency
LDB2 / TAPT1 / ZEB2P1	Amyotrophic lateral sclerosis	Syndromic osteochondrodysplasia
RIN3 / LGMN	*Paget's disease* *Chronic obstructive pulmonary disease* *Alzheimer's disease*	
MTHFSD / FOXL1 / FOXC2		Lymphedema-distichiasis

Underlined and italicized phenotypes have associations that exceed the threshold of genome-wide significance.

A

982 sJIA cases
8010 control subjects

B

Genotype samples with Illumina arrays and combined with *in silico* SNP genotype data

⬇

Stratify collection based on country of origin

⬇

Quality control operations (per stratum)

⬇

Imputation and association testing (per stratum)

⬇

Association meta-analysis

⬇

Compare genetic architecture of sJIA with other JIA subtypes
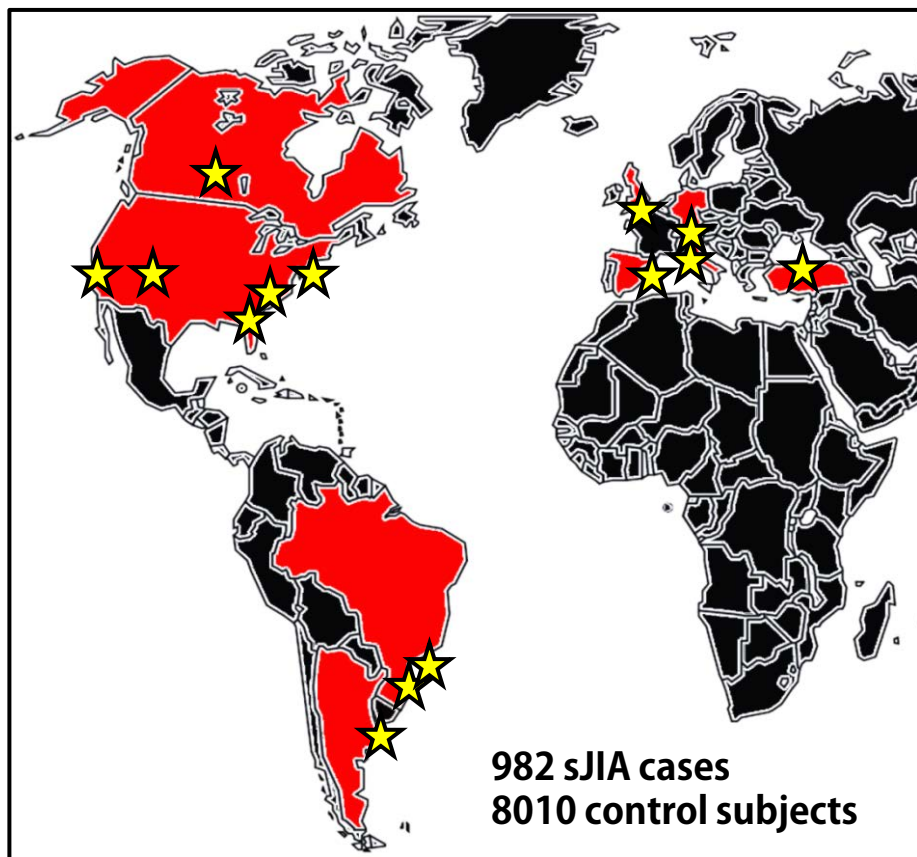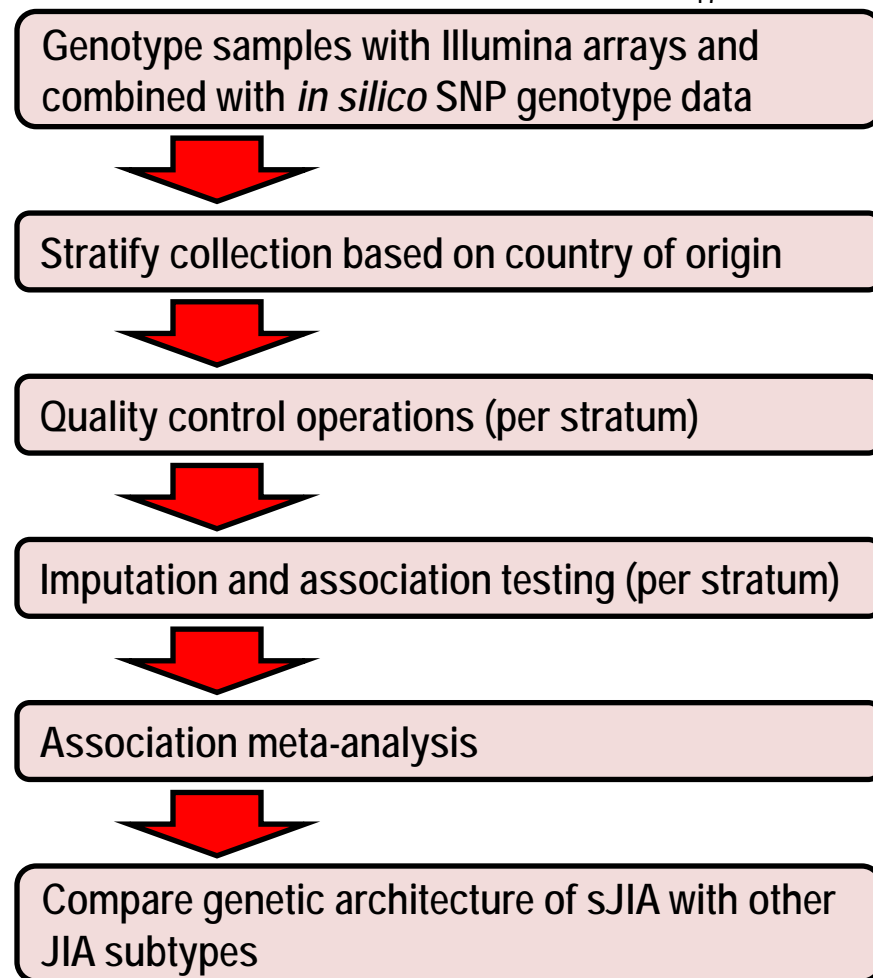
Figure S1. Summary of study design implemented by genomewide association study of systemic juvenile idiopathic arthritis. The International Childhood Arthritis Genetics Consortium GWAS of sJIA includes children from 14 referral centers (yellow stars) in 9 countries (red shading), as shown in **(A)**. The design of the study, which was stratified on the basis of geographic origin, is summarized in the flow chart in **(B)**.

Sample QC
Call rate > 98%
Mean heterozygosity ±3 SD
Relatedness (3rd degree)
Ancestral matching

Table S1

Phasing and imputation

Post Imputation QC
Info > 0.8
MAF case > 0.04

Table 1

SNP QC
Call rate > 0.97
MAF > 0.05
HWE p > 0.0001

Table S2

Association testing and meta-analysis

Post Meta-Analysis QC
I^2 < 0.7
N studies ≥ 4
n samples ≥ 2500
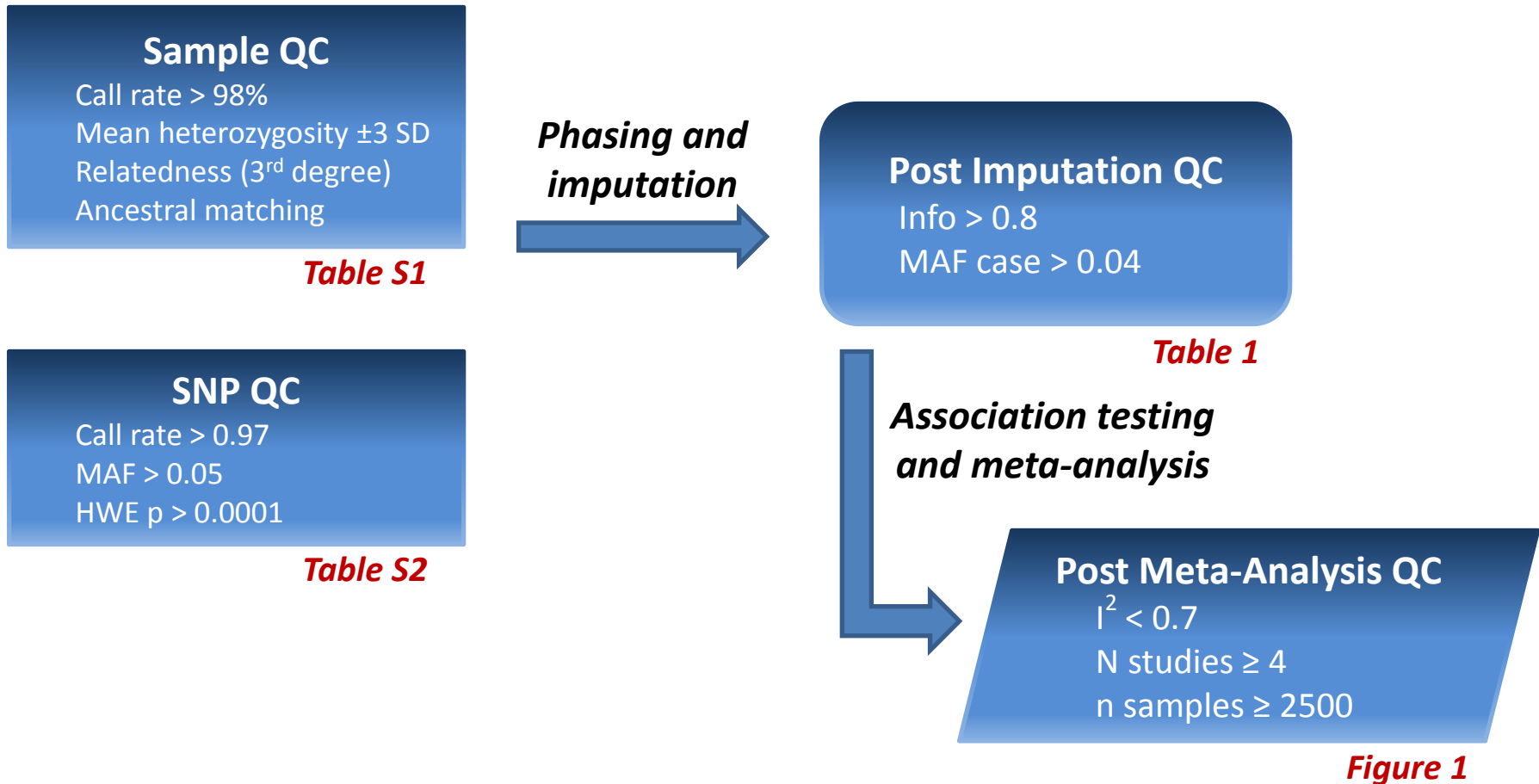
Figure 1

Figure S2. Summary of Quality Control Operations. Collections of directly genotyped sJIA cases and controls were combined with *in silico* SNP genotypes from additional control populations and were combined into 9 groups on the basis of geographic origin. Each collection was subjected to sample and SNP QC processes to produce 9 case-control strata. SNP imputation and association testing was performed separately in each population, and the genome-wide association results were meta-analyzed.
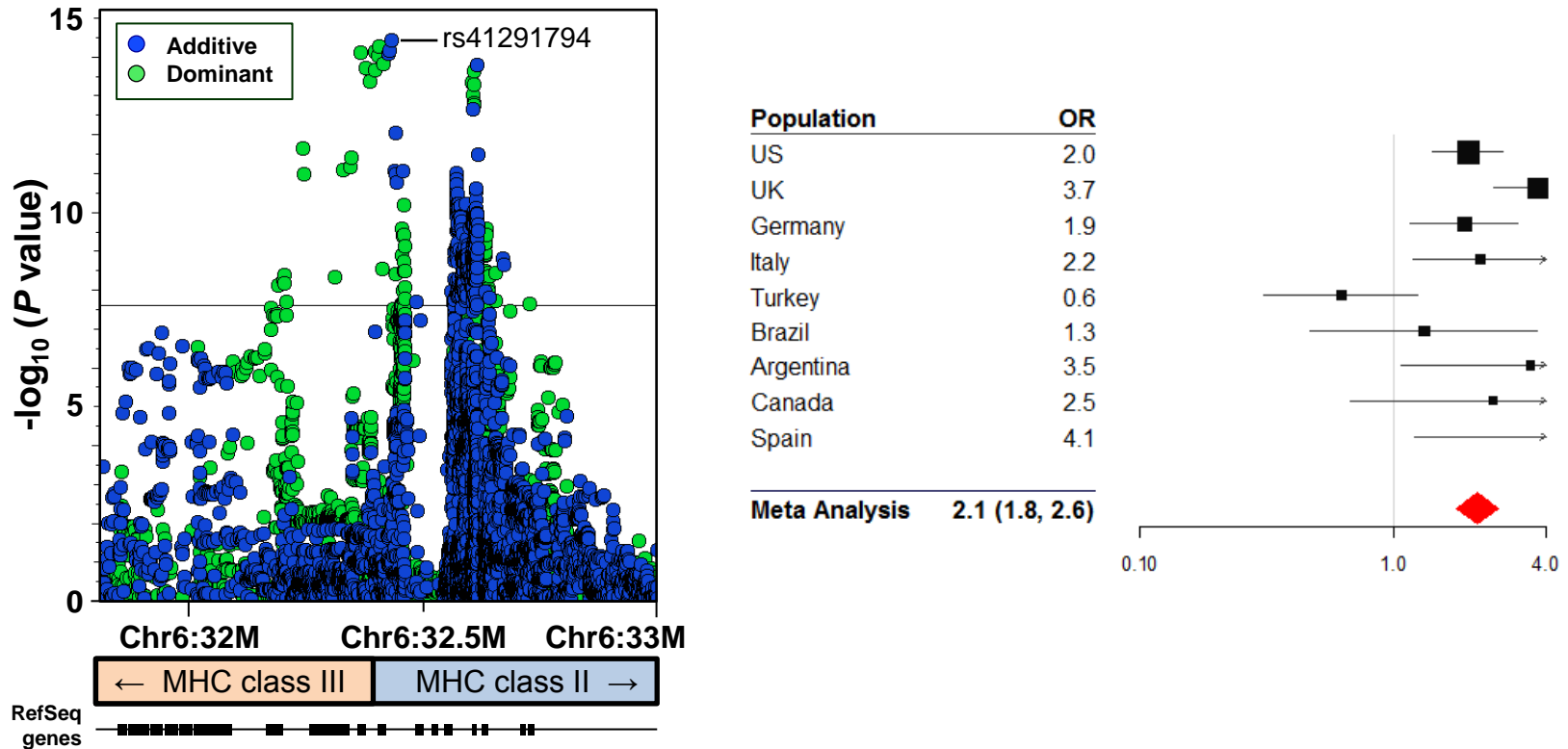
Figure S3. MHC locus is the strongest sJIA susceptibility locus. The regional association plot **(A)** of the MHC locus demonstrates a combination of additive (blue circles) and dominant (green circles) associations with sJIA. The threshold of genome-wide significance ($p < 2.5 \times 10^{-8}$) is depicted by the horizontal black line. The forest plots display the effect of the peak SNP, rs41291794, on sJIA risk. MHC, major histocompatibility complex. OR, odds ratio. sJIA, systemic juvenile idiopathic arthritis. SNP, single nucleotide polymorphism.
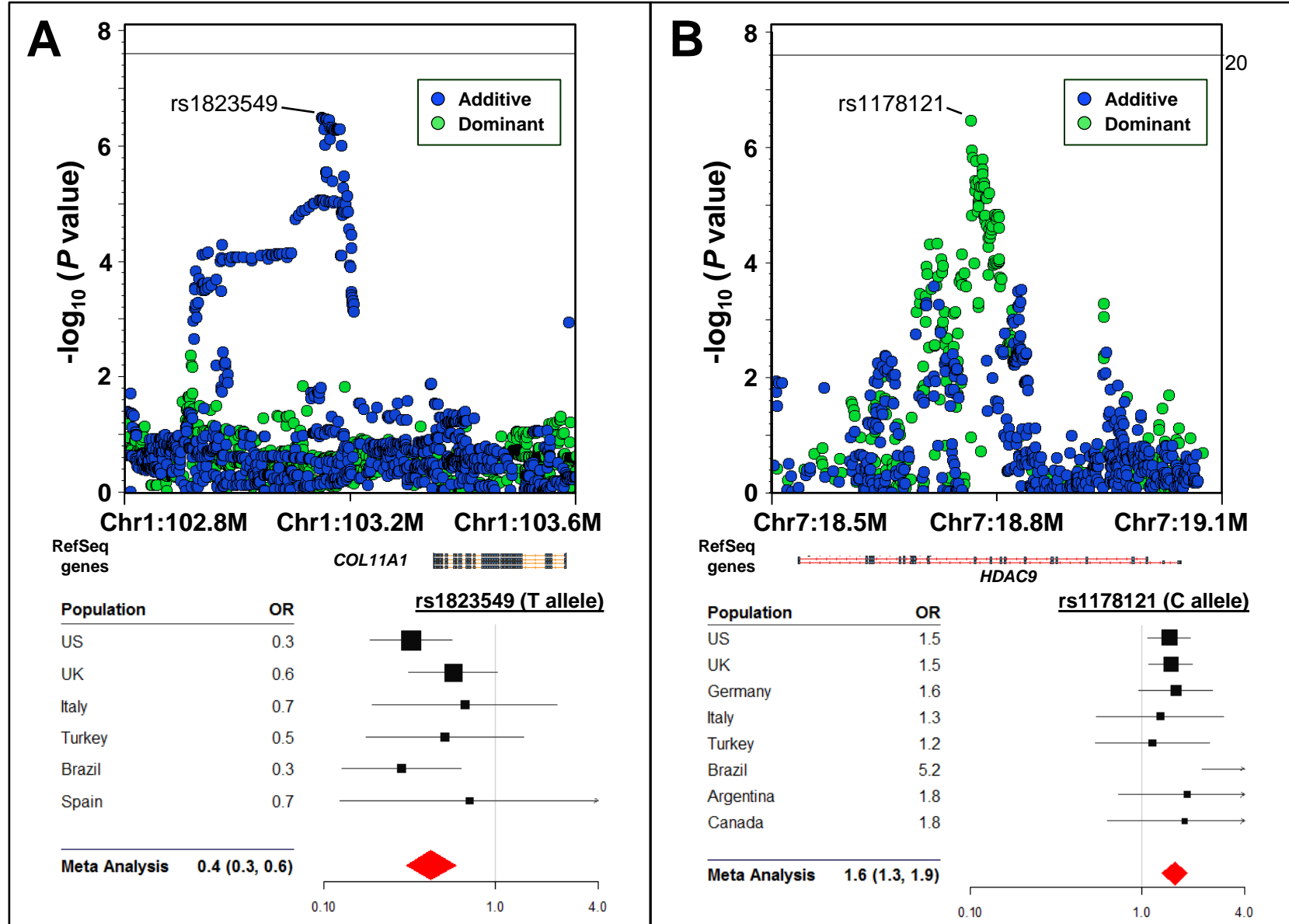
Figure S4. Regional association and forest plots of loci highly suggestive of association with sJIA. Regional association plots for susceptibility loci nearest to *COL11A1* **(A)** and *HDAC9* **(B)** demonstrate a combination of additive (blue circles) and dominant (green circles) associations with sJIA. The threshold of genome-wide significance ($p < 2.5 \times 10^{-8}$) is depicted by the horizontal black line. Forest plots display the effect of the peak SNP from each susceptibility locus in the study populations. OR, odds ratio. sJIA, systemic juvenile idiopathic arthritis. SNP, single nucleotide polymorphism.
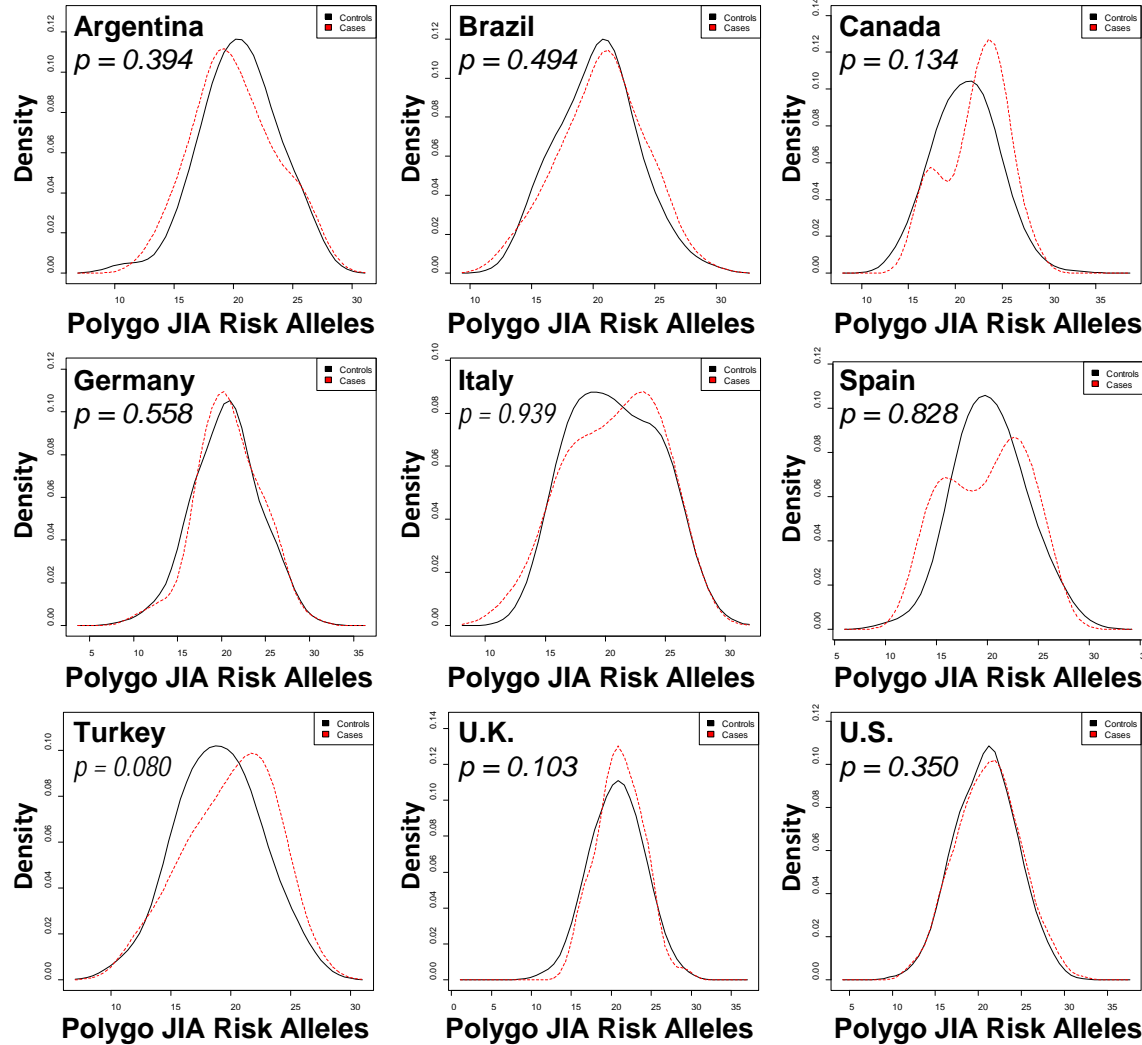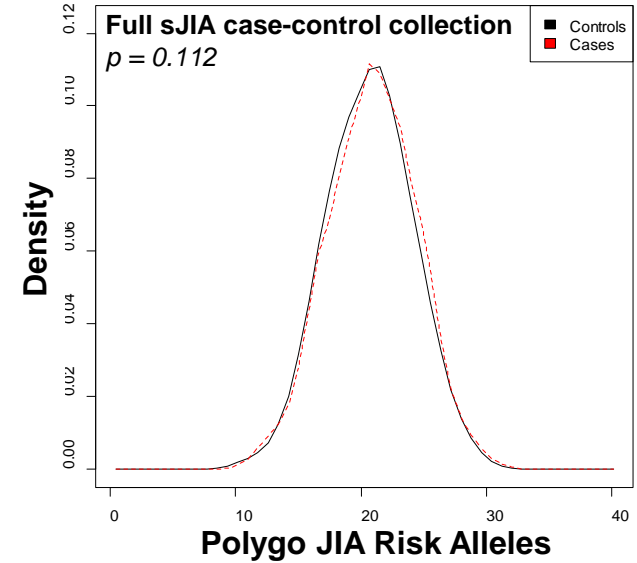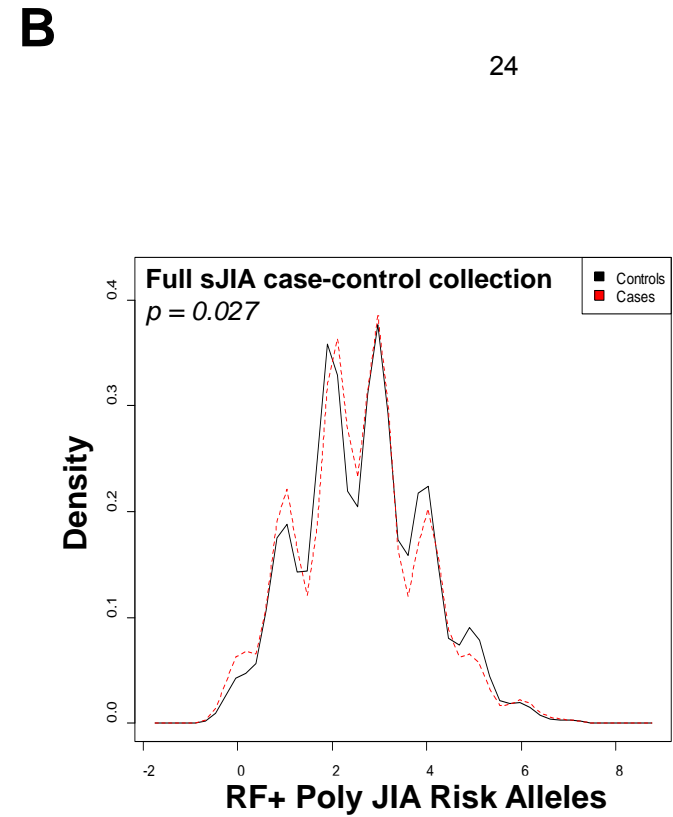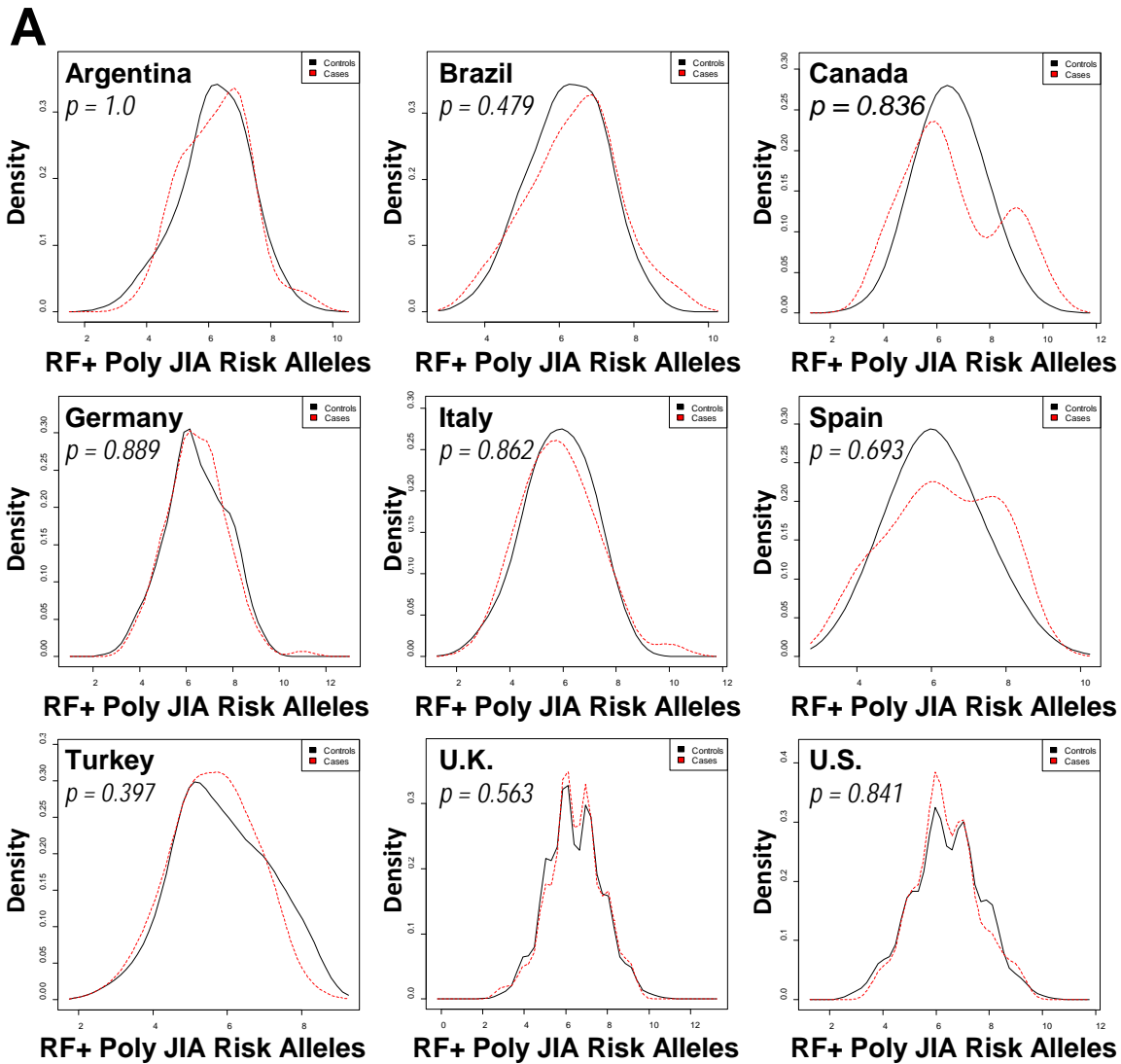
Figure S5. Polygo JIA risk allele counts in sJIA case-control collections.
Kernel density plots display the distributions of polygo JIA risk allele counts in 9 sJIA case-control populations **(A)** and in the case-control collection **(B)**. P values were calculated with the Wilcoxon Rank Sum test.
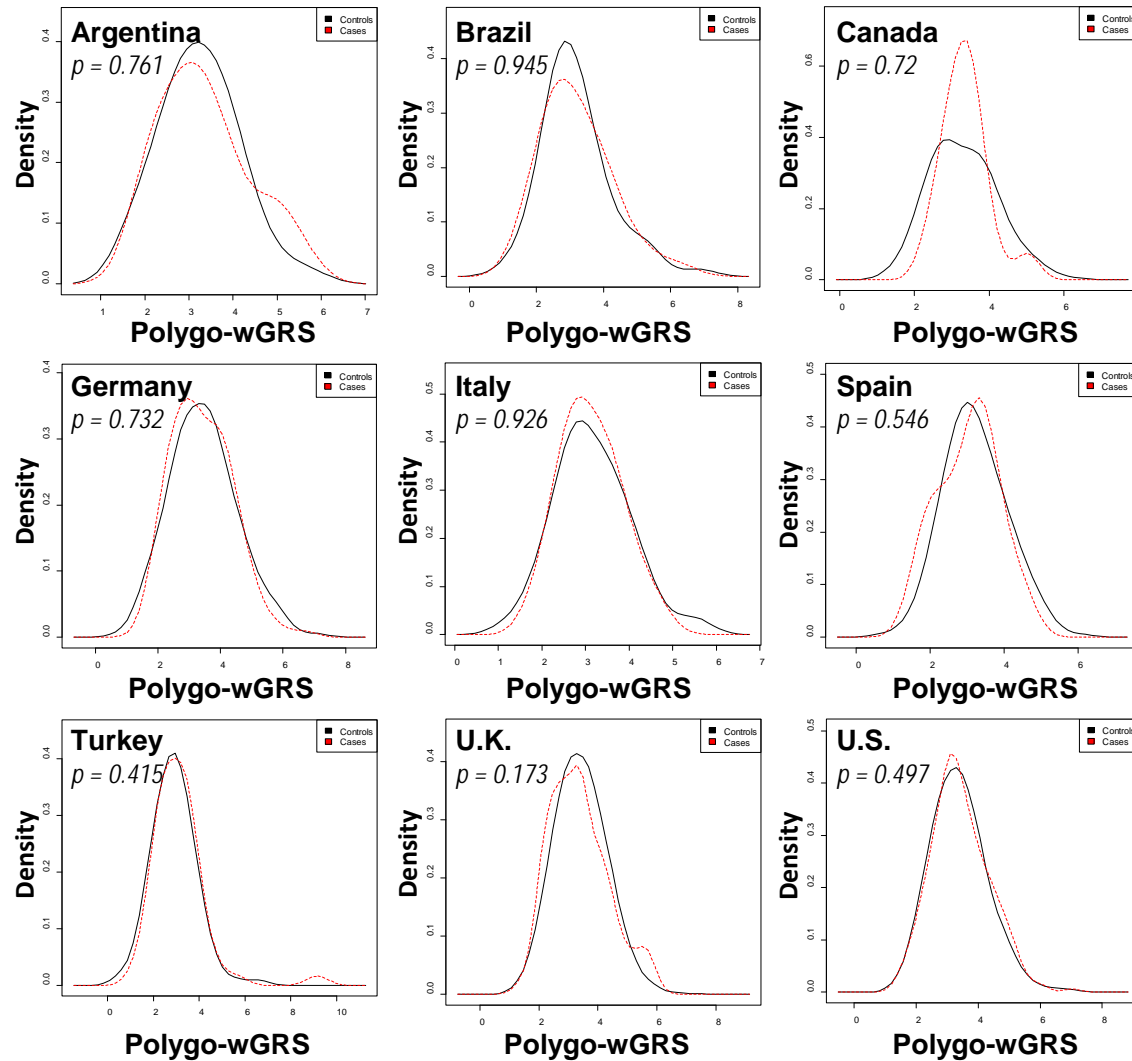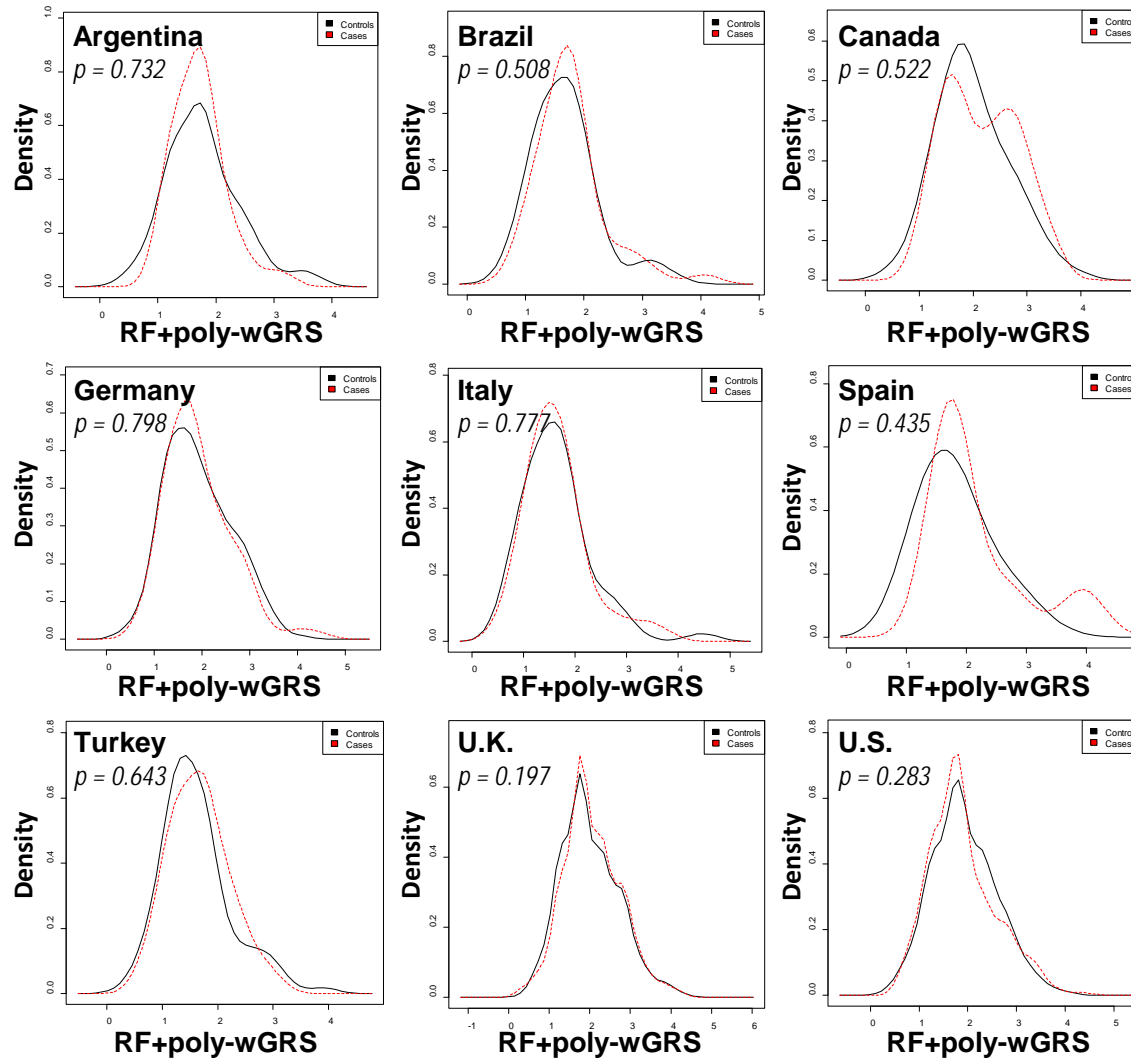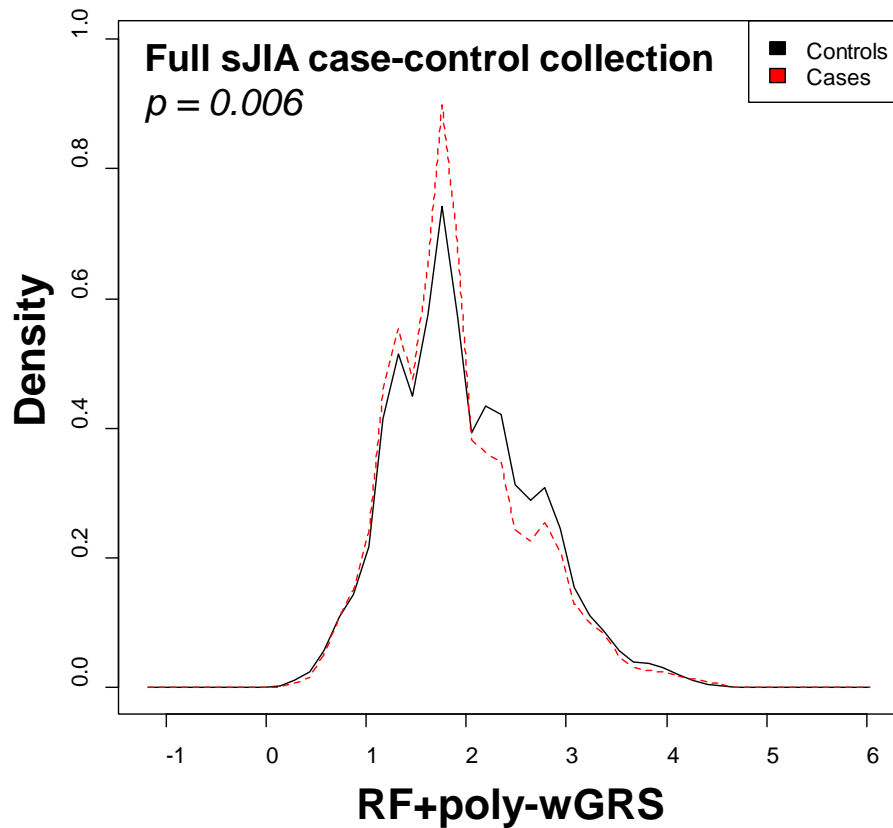
Figure S6. Polygo JIA weighted genetic risk scores (polygo-wGRS) in sJIA case-control collections. Kernel density plots display the distributions of polygo-wGRS in the 9 sJIA case-control populations. P values were calculated with the Wilcoxon Rank Sum test.
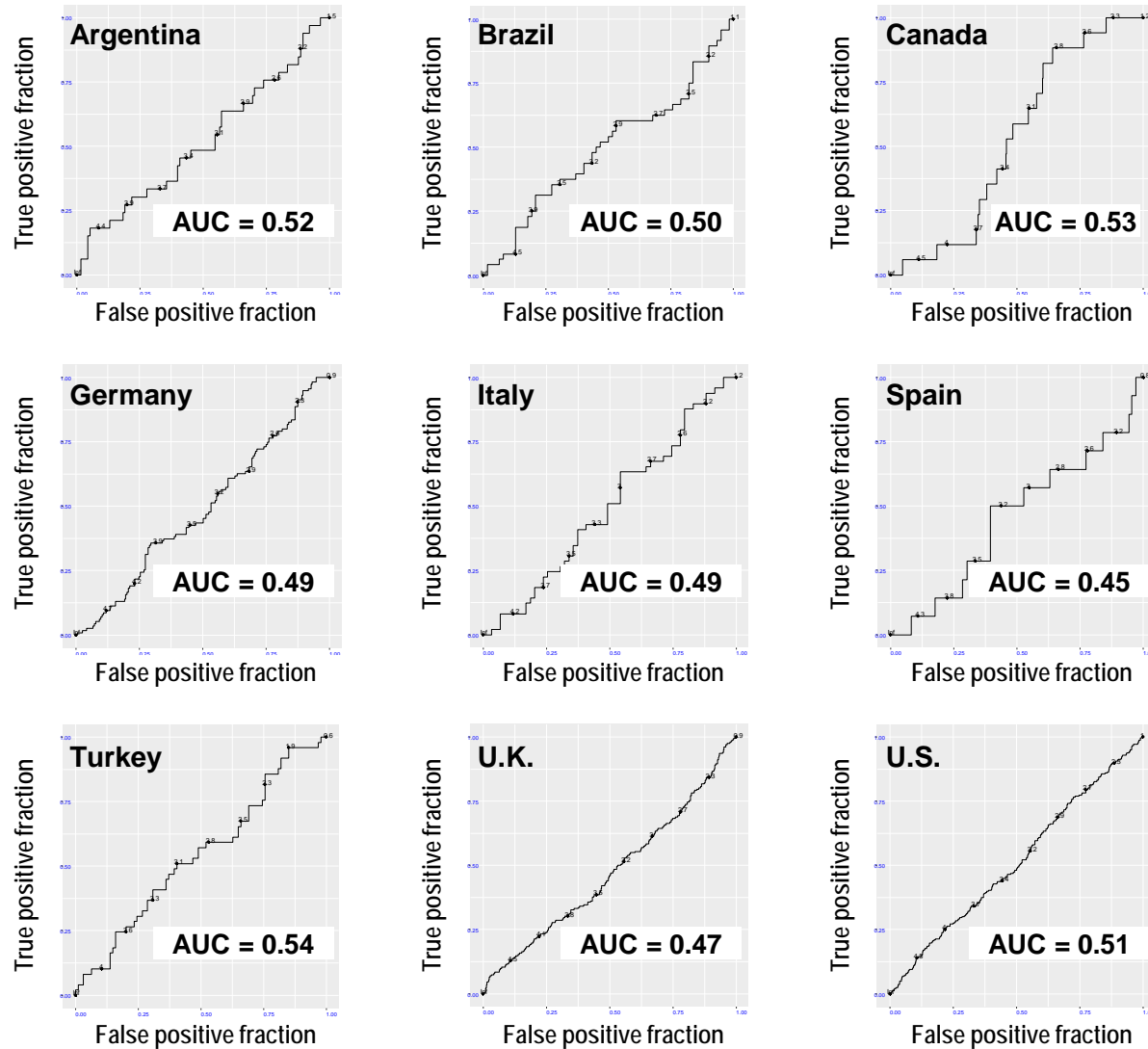
Figure S7. Predictive value of polygo JIA weighted genetic risk score (polygo-wGRS) in sJIA case-control collections. Receiver operator characteristic (ROC) curves with area under the curve (AUC) calculations demonstrate the performance of polygo-wGRS at predicting sJIA status in 9 sJIA case-control collections.

Figure S8. RF+ poly JIA risk allele counts in sJIA case-control collections.
Kernel density plots display the distributions of RF+poly JIA risk allele counts in
9 sJIA case-control populations **(A)** and in the full case-control collection **(B)**. P
values were calculated with the Wilcoxon Rank Sum test.

Figure S9. RF+ poly JIA weighted genetic risk scores (RF+poly-wGRS) in sJIA case-control collections. Kernel density plots display the distributions of RF+poly-wGRS in the 9 sJIA case-control populations. P values were calculated with the Wilcoxon Rank Sum test.
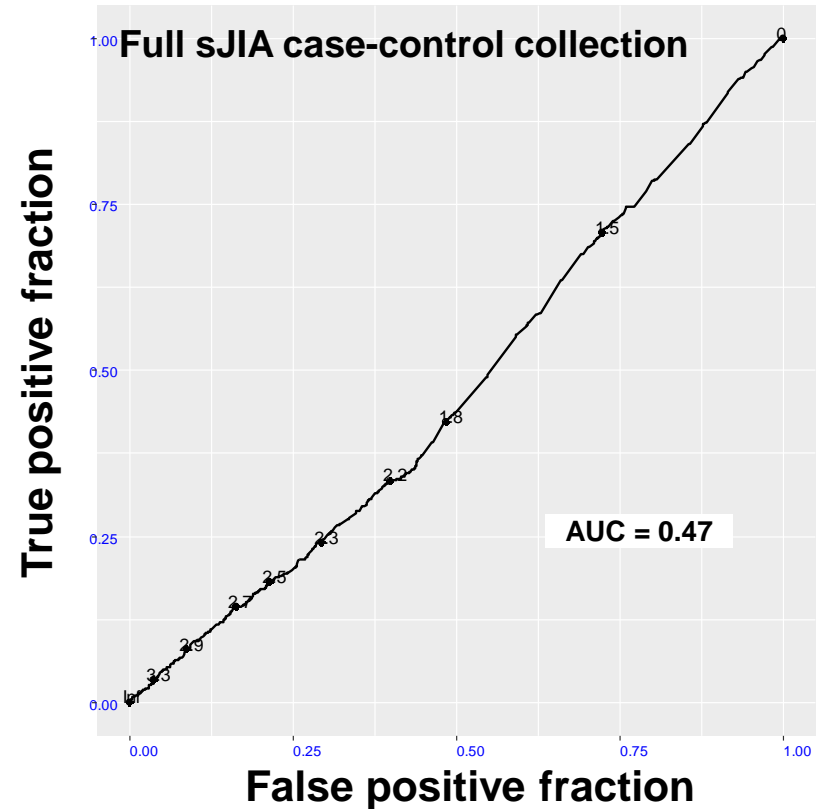
A

B

Figure S10. Examination of RF+ poly JIA weighted genetic risk score (RF+poly-wGRS) in full sJIA collection. Kernel density plot displays the distribution of RF+poly-wGRS in the full sJIA case-control collection **(A)**. P-value was calculated with the Wilcoxon Rank Sum test. In **Panel B**, receiver operator characteristic (ROC) curve with area under the curve (AUC) calculation demonstrates the performance of RF+poly-wGRS at predicting sJIA status in the full case-control collection.
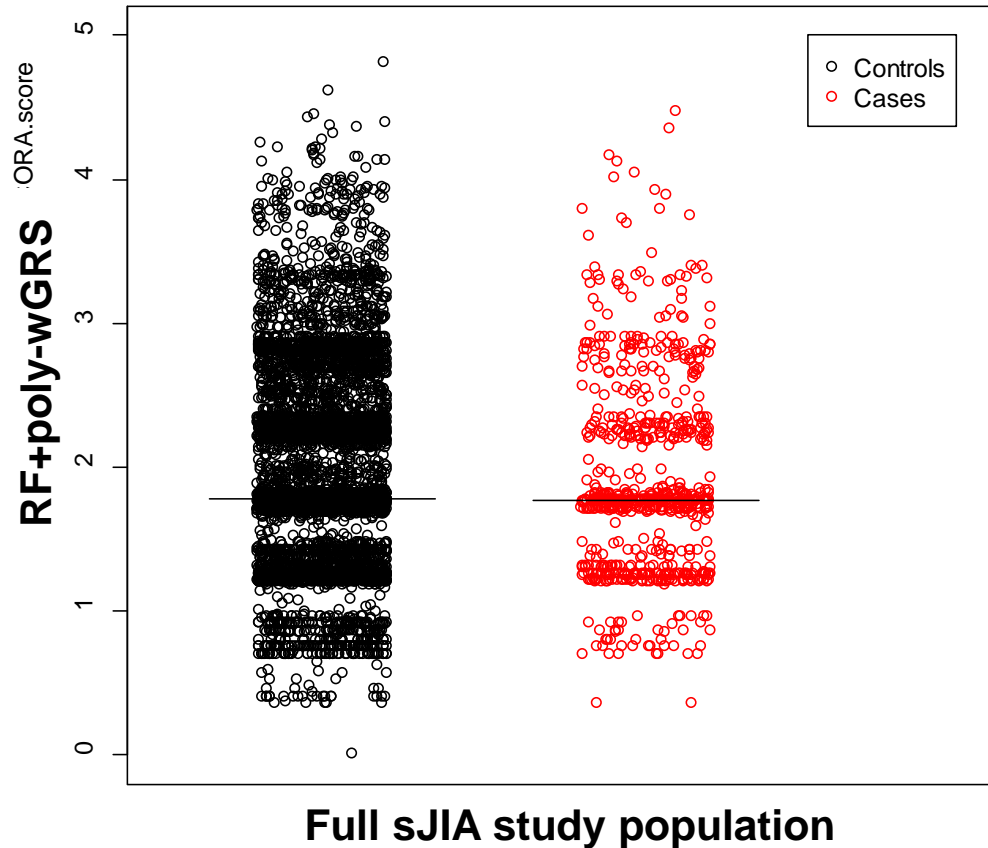
	Median	Mean
sJIA cases	1.77	1.91
Healthy controls	1.78	1.97

Figure S11. Scatter plot of RF+ poly JIA weighted genetic risk scores (RF+poly-wGRS) in sJIA cases and controls from the full study collection. Histograms demonstrate the distributions of RF+poly-wGRS in sJIA cases (red) and controls (black) from the full study collection. The horizontal lines represent the median values from each group, and the median and mean values are shown in the table to the right..
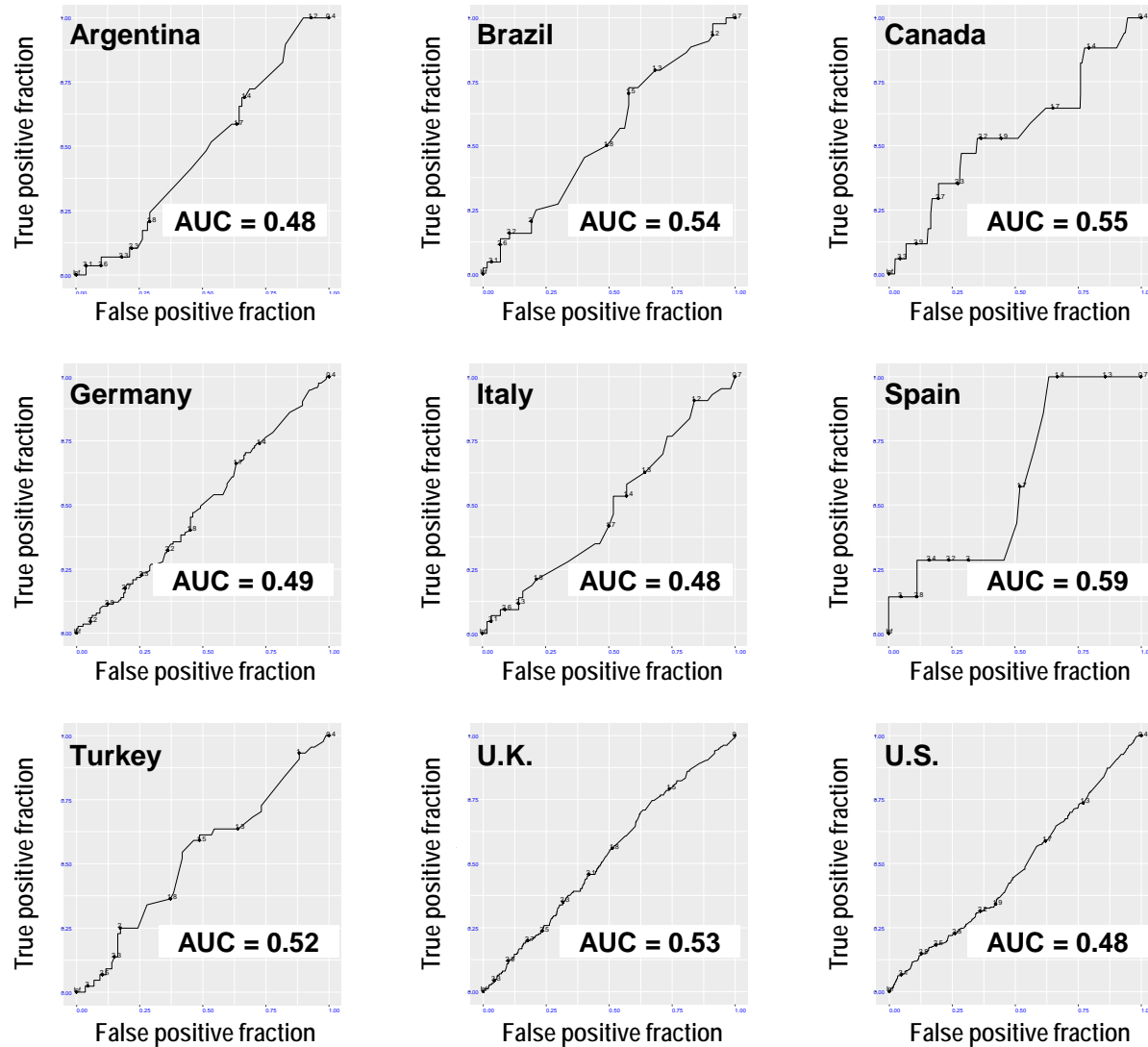
Figure S12. Predictive value of RF+ poly JIA weighted genetic risk score (RF+poly-wGRS) in sJIA collections. Receiver operator characteristic (ROC) curves with area under the curve (AUC) calculations demonstrate the performance of RF+poly-wGRS at predicting sJIA status in 9 sJIA case-control collections.