

Supplementary Table 1. Summary of SNP and sample quality control for each genotype array used in Phase 1 and 2

	Phase 1			Phase 2a PromiSERA Sequencing	Phase 2b	
	OmniExpressExome	CoreExome	Immunochip		1M-Duo-v3	Omni1-Quad-v1-0
Genotyped SNPs	964193	547644	196524	NA	1199187	1140419
Failed	88939	26265	10051	NA	64730	1900001
MAF<1%	248861	237203	49334	NA	154023	162448
Final SNP Total for imputation	626393	284176	137139	NA	980434	787970
SNPs with MAF>5% & INFO>0.8 post imputation	5707255	5690412	926912	NA	5742906	5689816
Genotyped Samples	1152	694	560	449 ^a	263	2023
Call rate	7	3	10	NA	0	15
Gender	18	0	2	NA	0	5
IBD (Relatedness/Duplicate samples)	18	3	4	NA	0	34
PCA (Non-European ancestry)	109	101	20	1	18	69
non-MTX	83	110	261	0	152	1808
High dose steroid	0	0	102	0	0	0
Incomplete clinical data	146	24	9	20	8	0
Final Sample Total	823	453	148	429	85	92

^a Samples sequenced, not genotyped

Supplementary Table 2. Summary of the Methotrexate metabolism candidate genes selection

Gene	cytoband	Pathway	Full name	Position Start (bp)	Position End (bp)	SNPs Tested
<i>MTHFR</i>	1p36.22	Folate metabolism	methylenetetrahydrofolate reductase (NAD(P)H)	11845787	11866160	69
<i>AMPD1</i>	1p13.2	Adenosine metabolism	adenosine A3 receptor	112025970	112106597	217
<i>ADORA3</i>	1p13.2	Adenosine signalling	adenosine monophosphate deaminase 1	115215719	115238239	43
<i>ADORA1</i>	1q32.1	Adenosine signalling	adenosine A1 receptor 5-methyltetrahydrofolate-homocysteine	203096836	203136533	76
<i>MTR</i>	1q43	Homocysteine metabolism	methyltransferase 5-aminoimidazole-4-carboxamide ribonucleotide	236958581	237067281	185
<i>ATIC</i>	2q35	Adenosine accumulation	formyltransferase/IMP cyclohydrolase	216176679	216214496	107
<i>PPAT</i>	4q12	De novo purine synthesis	phosphoribosyl pyrophosphate amidotransferase	57259528	57301802	80
<i>ABCG2</i>	4q22.1	MTX transport	ATP-binding cassette, sub-family G (WHITE), member 2 5-methyltetrahydrofolate-homocysteine	89011416	89152474	329
<i>MTRR</i>	5p15.31	Homocysteine metabolism	methyltransferase reductase	7869217	7901237	80
<i>DHFR</i>	5q14.1	Folate metabolism	dihydrofolate reductase	79922045	79950800	140
<i>TPMT</i>	6p22.3	Purine metabolism	thiopurine S-methyltransferase solute carrier family 29 (nucleoside transporters),	18128542	18155374	52
<i>SLC29A1</i>	6p21.1	Adenosine transport	member 1	44187242	44201888	17
<i>NT5E</i>	6q14.3	Adenosine metabolism	5'-nucleotidase, ecto (CD73)	86159302	86205509	48
<i>ABCB1</i>	7q21.12	MTX transport	ATP-binding cassette, sub-family B (MDR/TAP), member 1 gamma-glutamyl hydrolase (conjugase,	87133179	87342639	215
<i>GGH</i>	8q12.3	MTX metabolism	folylpolygammaglutamyl hydrolase)	63927638	63951610	84
<i>FPGS</i>	9q34.11	MTX metabolism	folylpolyglutamate synthase	130565154	130576556	7
<i>ADK</i>	10q22.2	Adenosine metabolism	adenosine kinase	75910943	76469061	643
<i>ABCC2</i>	10q24.2	MTX transport	ATP-binding cassette, sub-family C (CFTR/MRP), member 2 methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1, methenyltetrahydrofolate cyclohydrolase,	101542463	101611662	100
<i>MTHFD1</i>	14q23.2	Folate metabolism	formyltetrahydrofolate synthetase 5,10-methenyltetrahydrofolate synthetase (5-	64854759	64926725	115
<i>MTHFS</i>	15q25.1	Folate metabolism	formyltetrahydrofolate cyclo-ligase)	80135889	80189627	117
<i>ADORA2B</i>	17p12	Adenosine signalling	adenosine A2b receptor	15848231	15879210	10
<i>SHMT1</i>	17p11.2	Folate metabolism	serine hydroxymethyltransferase 1 (soluble)	18231187	18266856	91
<i>TYMS</i>	18p11.32	Folate metabolism	thymidylate synthetase inosine triphosphatase (nucleoside triphosphate	657604	673499	64
<i>ITPA</i>	20p13	Purine metabolism	pyrophosphatase)	3189514	3204516	63
<i>ADA</i>	20q13.12	Adenosine accumulation	adenosine deaminase phosphoribosylglycinamide formyltransferase, phosphoribosylglycinamide synthetase,	43248163	43280376	41
<i>GART</i>	21q22.11	Adenosine accumulation	phosphoribosylaminoimidazole synthetase	34876238	34915198	40
<i>CBS</i>	21q22.3	Homocysteine metabolism	cystathionine-beta-synthase	44473301	44496472	68
<i>SLC19A1</i>	21q22.3	MTX transport	solute carrier family 19 (folate transporter), member 1	46934629	46962385	56
<i>ADORA2A</i>	22q11.23	Adenosine signalling	adenosine A2a receptor	24823530	24838325	11

Supplementary Table 3. Mean baseline and follow-up measures for each of the 4 traits by study

Study	Origin	Genotype Array	N	Mean (SD) clinical measurement													
				DAS28				SJC28				TJC28				CRP	
				Baseline		Follow-up		Baseline		Follow-up		Baseline		Follow-up		Baseline	Follow-up
Phase 1																	
YEAR	UK	OmniExpressExome-8v1-2	343	5.0	(1.2)	3.8	(1.4)	8.7	(6.7)	3.6	(4.6)	10.8	(7.8)	6.9	(7.8)	30.7	(39.4)
TEAR ^a	US	OmniExpressExome-8v1-2	117	5.6	(1.0)	4.0	(1.4)	12.4	(5.8)	5.7	(5.5)	13.7	(6.8)	6.5	(6.8)	15.2	(23.6)
SWEFOT	Sweden	OmniExpressExome-8v1-2	325	5.1	(0.9)	3.6	(1.2)	10.6	(5.2)	4.7	(4.8)	9.4	(6.0)	4.5	(4.9)	34.9	(39.4)
Netherlands	Netherlands	OmniExpressExome-8v1-2	38	4.6	(1.2)	3.5	(1.2)	7.9	(5.6)	3.7	(3.8)	10.3	(7.4)	6.0	(6.3)	15.9	(22.1)
RAMS	UK	CoreExome-24-v1-0	274	4.4	(1.2)	3.4	(1.1)	7.5	(6.1)	3.1	(4.1)	9.5	(7.8)	5.3	(6.0)	14.4	(21.7)
IDEA	UK	CoreExome-24-v1-0	29	4.9	(1.3)	3.0	(1.2)	6.8	(4.7)	1.7	(2.7)	11.3	(7.5)	3.7	(6.0)	32.4	(48.1)
IACON	UK	CoreExome-24-v1-0	128	4.3	(1.3)	3.0	(1.2)	5.6	(5.4)	1.6	(2.5)	8.3	(7.4)	3.6	(5.2)	18.7	(25.3)
EMPIRE	UK	CoreExome-24-v1-0	22	4.2	(0.9)	2.9	(1.2)	3.2	(4.6)	1.2	(1.9)	8.6	(5.5)	4.7	(5.1)	15.5	(20.8)
CARDERA Trials ^a	UK	Immunochip	148	5.8	(1.1)	4.4	(1.3)	10.4	(6.5)	6.4	(7.0)	13.6	(7.6)	7.0	(6.7)		
Phase 2a																	
PromiSERA	UK	Sequencing at mean depth 0.5x	429	4.8	(1.2)	3.2	(1.2)	7.6	(5.5)	2.3	(3.6)	9.5	(7.2)	4.2	(5.4)	30.3	(39.4)
Phase 2b																	
AMBITION	International	1M-Duo-v3	85	6.0	(0.8)	4.3	(1.4)	14.1	(5.3)	7.1	(6.4)	17.3	(6.8)	9.3	(8.0)	34.8	(39.7)
MabThera Trials	International	Omni1-Quad-v1-0	32	5.7	(0.9)	3.7	(1.5)	11.5	(4.6)	4.7	(5.4)	15.0	(6.8)	6.4	(7.6)	28.9	(26.7)
Ocrelizumab Trials	International	Omni1-Quad-v1-0	60	6.0	(0.9)	4.0	(1.2)	13.3	(5.8)	5.0	(4.0)	16.9	(6.6)	6.2	(6.0)	34.3	(28.1)

^a CRP not available, DAS28 calculated using ESR

RS12608776:	19	49731824	G	0.180	0.042	1.50E-05	G	-0.142	0.059	1.63E-02	-0.023	0.121	8.52E-01
RS11878934:	19	49732614	C	0.151	0.039	1.30E-04	C	-0.139	0.057	1.53E-02	0.006	0.119	9.60E-01
RS61184327:	19	49733234	T	0.150	0.039	1.31E-04	T	-0.139	0.057	1.53E-02	0.004	0.118	9.70E-01
RS12610107:	19	49735062	A	0.146	0.039	1.62E-04	A	-0.143	0.057	1.29E-02	0.001	0.115	9.96E-01
RS35785122:	19	49735107	T	0.180	0.041	1.16E-05	T	-0.146	0.058	1.25E-02	-0.030	0.118	8.02E-01
RS56758737:	19	49735111	T	0.181	0.041	9.87E-06	T	-0.147	0.058	1.20E-02	-0.028	0.118	8.11E-01
RS58106112:	19	49735271	A	0.182	0.041	9.55E-06	A	-0.147	0.058	1.20E-02	-0.027	0.119	8.17E-01
RS12610169:	19	49735520	T	0.181	0.041	1.06E-05	T	-0.146	0.058	1.28E-02	-0.027	0.119	8.19E-01
RS59251910:	19	49735637	T	0.181	0.041	1.03E-05	T	-0.146	0.058	1.28E-02	-0.026	0.119	8.24E-01
RS56674801:	19	49735940	G	0.182	0.041	9.65E-06	G	-0.146	0.058	1.24E-02	-0.024	0.119	8.37E-01
RS73580436:	19	49736660	G	0.183	0.041	8.24E-06	G	-0.146	0.058	1.23E-02	-0.019	0.120	8.72E-01
RS11758124:	19	49737476	G	0.202	0.042	1.78E-06	G	-0.140	0.059	1.78E-02	0.002	0.125	9.89E-01
RS11758134:	19	49737486	G	0.205	0.042	1.44E-06	G	-0.149	0.059	1.23E-02	0.004	0.126	9.76E-01
RS11699647:	20	22949613	A	0.159	0.044	2.69E-04	A	0.023	0.069	7.40E-01	0.325	0.153	3.35E-02
RS92672722:	20	22997422	T	0.140	0.033	1.84E-05	T	-0.023	0.052	6.63E-01	0.250	0.102	1.43E-02
RS36011369:	20	23006996	T	0.136	0.033	3.01E-05	T	-0.001	0.053	9.88E-01	0.216	0.103	3.60E-02
RS13045080:	20	23009546	G	0.134	0.033	3.74E-05	G	0.000	0.053	9.93E-01	0.214	0.103	3.80E-02
RS11905464:	20	23012830	G	0.135	0.033	3.21E-05	G	0.000	0.052	9.93E-01	0.213	0.103	3.85E-02
RS31761232:	20	23027413	G	0.145	0.032	7.74E-06	G	0.016	0.053	7.61E-01	0.217	0.103	3.44E-02
RS10425792:	20	23028724	A	0.146	0.032	6.92E-06	A	0.016	0.053	7.57E-01	0.240	0.103	1.99E-02
RS27498122:	20	23062927	A	0.127	0.036	4.55E-04	A	0.055	0.061	3.73E-01	0.139	0.113	2.21E-01
RS28369074:	21	40504673	A	-0.109	0.028	1.39E-04	A	-0.027	0.048	5.68E-01	-0.081	0.089	3.65E-01
RS10783064:	21	40507612	G	-0.126	0.028	5.80E-06	G	-0.055	0.046	2.38E-01	-0.061	0.091	5.00E-01
RS56113957:	21	40509103	A	-0.127	0.028	4.69E-06	A	-0.053	0.046	2.57E-01	-0.059	0.091	5.13E-01
RS28369154:	21	40509189	T	-0.128	0.028	4.46E-06	T	-0.053	0.046	2.56E-01	-0.060	0.091	5.09E-01
RS28369174:	21	40509990	C	-0.128	0.028	4.84E-06	C	-0.055	0.046	2.31E-01	-0.073	0.092	4.27E-01
RS28369204:	21	40512918	G	-0.103	0.026	9.38E-05	G	-0.033	0.043	4.37E-01	0.053	0.083	5.25E-01
RS28369774:	21	40666066	C	-0.086	0.026	8.35E-04	C	-0.024	0.042	5.70E-01	0.014	0.084	8.70E-01
RS72826244:	21	40667040	T	-0.086	0.026	8.34E-04	T	-0.024	0.042	5.69E-01	0.014	0.084	8.69E-01
RS34038277:	21	40699847	G	-0.086	0.026	9.14E-04	G	-0.013	0.042	7.57E-01	0.029	0.087	7.41E-01

Supplementary Table 8. DAS28 results for all SNPs with P<0.0001 in a genome-wide study of methotrexate response in Indian rheumatoid arthritis patients (Senapati et al.)
Effect direction is in relation to effect allele: + indicates improvement in DAS28 score/response, - indicates increase in DAS score/non-response.

Marker	Chr	Position	Senapati et al.	P-value	Effect Allele	DAS28		Effect Direction		gene
						β	P-value	Senapati et al.	This Study	
RS3820304	1	13938788	0.0007	G	0.029	4.45E-01	-	-	-	PDPN
RS12746273	1	23950177	0.001	T	0.033	4.37E-01	+	-	-	
RS12142410	1	30636759	0.0001	G	0.049	6.65E-01	-	-	-	
RS10493098	1	42261889	0.0002	C	0.032	3.64E-01	-	-	-	HIVEP3
RS332823	1	61674052	0.0008	G	0.004	9.04E-01	+	-	-	NFIA
RS855849	1	64353473	0.001	A	0.002	9.57E-01	+	-	-	ROR1
RS7511712	1	118279908	0.0005	C	-0.007	8.52E-01	+	+	-	
RS3754123	1	118319990	0.0002	G	-0.030	4.09E-01	+	+	+	LOC100131261
RS3754125	1	118323282	0.0002	C	-0.030	3.99E-01	+	+	-	
RS12128109	1	153212668	0.0008	A	0.016	6.69E-01	+	-	-	
RS1317986	1	159955432	0.0004	A	0.004	9.18E-01	-	-	-	
RS6699725	1	161703525	0.0004	T	0.067	2.10E-01	-	-	-	
RS3748699	1	165877751	0.0007	A	-0.031	5.35E-01	-	+	-	UCK2
RS16852868	1	165881969	0.0005	C	-0.031	5.32E-01	-	+	-	
RS3010141	1	195854742	0.0009	T	-0.078	6.73E-02	+	+	-	
RS4423076	1	203123837	0.0005	T	0.071	1.77E-01	+	-	-	ADORA1
RS6703183	1	209712889	0.0006	C	0.066	7.93E-02	+	-	-	
RS9424584	1	232840697	0.0001	C	-0.004	9.45E-01	-	+	-	
RS499370	1	238751937	0.0005	A	-0.008	8.31E-01	-	+	-	
RS947103	1	245766651	0.0006	A	0.025	4.82E-01	+	-	-	KIF26B
RS1437701	2	4173729	0.0006	T	0.068	5.32E-02	-	-	-	
RS10204428	2	20084133	0.0006	G	0.025	6.82E-01	+	-	-	FLJ12334
RS13036246	2	25532969	0.0005	C	0.025	4.62E-01	+	-	-	DNMT3A
RS6722613	2	25539357	0.0001	G	0.050	3.61E-01	+	-	-	DNMT3A
RS10208987	2	44043135	0.0003	G	0.055	3.71E-01	-	-	-	ABCG5
RS4148189	2	44047530	0.0005	T	0.095	8.22E-02	-	-	-	ABCG5
RS6705555	2	72062531	0.0005	T	0.022	5.54E-01	+	-	-	
RS2861609	2	78633880	0.0005	A	-0.012	8.38E-01	+	+	-	
RS1455390	2	78655712	0.0007	G	-0.014	8.12E-01	+	+	-	
RS724710	2	111907691	0.0007	T	-0.046	4.13E-01	-	+	-	BCL2L11
RS1878114	2	118355321	0.0005	C	-0.013	8.31E-01	-	+	-	
RS4849589	2	118356511	0.0004	T	-0.013	8.33E-01	-	+	-	
RS12691828	2	133530648	0.0002	G	0.042	2.44E-01	-	-	-	NCKAP5
RS12466096	2	134861399	0.0006	C	-0.008	8.47E-01	-	+	-	
RS6749316	2	138073500	0.0009	T	-0.045	2.00E-01	+	+	-	THSD7B
RS10206675	2	154440521	0.0007	G	-0.014	8.35E-01	-	+	-	
RS1401750	2	154453616	0.0009	A	-0.006	8.90E-01	-	+	-	
RS4335901	2	154460874	0.0009	G	-0.011	7.68E-01	-	+	-	
RS1519635	2	154481164	0.0004	G	-0.001	9.89E-01	-	+	-	
RS908919	2	154519277	0.0007	T	-0.046	2.49E-01	-	+	-	
RS2881873	2	154524124	0.0008	T	0.031	5.22E-01	-	-	-	
RS1435004	2	163657083	0.0007	A	-0.026	5.46E-01	-	+	-	KCNH7
RS13018302	2	163703613	0.0006	C	-0.058	1.46E-01	-	+	-	
RS3817135	2	165753118	0.0005	G	-0.002	9.46E-01	+	+	-	
RS16867139	2	180872427	0.0009	G	-0.045	5.91E-01	+	+	-	
RS10188385	2	185949889	0.0003	C	0.065	1.20E-01	+	-	-	
RS9288109	2	186025368	0.0005	C	0.086	2.03E-01	+	-	-	
RS10388361	2	186031490	0.0004	A	0.090	2.21E-01	+	-	-	
RS6795047	3	1933220	0.0008	T	-0.025	6.38E-01	-	+	-	
RS1387091	3	1988126	0.0008	G	-0.039	3.95E-01	-	+	-	
RS13065523	3	4274646	0.0003	T	-0.057	1.01E-01	-	+	-	
RS1876613	3	4282950	0.0003	C	-0.059	8.92E-02	-	+	-	
RS12486791	3	4325300	0.000094	C	-0.056	1.12E-01	-	+	-	
RS3804989	3	4728008	0.0003	G	-0.031	3.71E-01	-	+	-	ITPR1
RS6803471	3	4732040	0.0008	G	-0.040	2.48E-01	-	+	-	ITPR1
RS9311395	3	4741821	0.0005	A	-0.041	2.42E-01	-	+	-	ITPR1
RS155421	3	6464294	0.0005	T	0.008	8.21E-01	+	-	-	
RS7645290	3	15855531	0.0006	C	0.063	1.70E-01	+	-	-	ANKRD28
RS6764520	3	54591243	0.001	G	-0.018	6.59E-01	-	+	-	CACNA2D3
RS3772985	3	58186719	0.0003	A	-0.007	8.94E-01	-	+	-	DNASE1L3
RS1349008	3	76721413	0.001	G	-0.038	4.70E-01	-	+	-	ROBO2
RS4350947	3	121744849	0.0002	C	0.004	9.30E-01	-	-	-	

RS931574	3	123098965	0.0005	T	0.010	8.46E-01	-	-	ADCY5
RS12636883	3	132429522	0.0006	A	-0.020	8.11E-01	-	+	NPHP3-ACAD11
RS2369832	3	132437390	0.0008	T	-0.012	7.94E-01	-	+	NPHP3-ACAD11
RS3860503	3	132438301	0.0004	C	-0.014	7.52E-01	-	+	NPHP3-ACAD11
RS13078077	3	143853149	0.0005	G	-0.024	5.07E-01	+	+	
RS6440786	3	151510257	0.0002	G	-0.009	8.44E-01	-	+	
RS819851	3	155706888	0.0004	C	-0.117	9.36E-02	-	+	
RS7651855	3	160412175	0.000071	T	0.000	9.97E-01	-	-	
RS1378661	3	160424299	0.00008	T	0.007	8.96E-01	-	-	
RS7624766	3	160429869	4.80E-07	G	0.014	8.42E-01	-	-	
RS6793037	3	160447946	0.0002	C	0.073	3.44E-01	-	-	
RS13061243	3	165859107	0.0007	C	-0.017	6.41E-01	-	+	
RS6982469	3	168414697	0.0009	C	-0.027	4.48E-01	+	+	EGFEM1P
RS790003	3	194341327	0.0006	A	-0.019	5.98E-01	-	+	TMEM44
RS3901794	4	7149008	0.0007	T	0.042	2.39E-01	-	-	
RS11724494	4	7153642	0.0002	T	-0.057	1.13E-01	-	+	
RS6826086	4	21614663	0.0008	T	-0.110	1.90E-02	+	+	KCNIP4
RS10516395	4	21628375	0.0007	C	-0.087	1.20E-01	+	+	KCNIP4
RS13152723	4	22203707	0.0005	G	-0.014	7.48E-01	-	+	
RS4697041	4	23603378	0.0003	A	-0.011	8.69E-01	-	+	
RS880358	4	56276478	0.0009	T	-0.002	9.65E-01	+	+	TMEM165
RS2412664	4	56457387	0.001	A	0.008	8.56E-01	+	-	PDCL2
RS1355803	4	60534555	0.0002	C	0.019	6.99E-01	+	-	
RS17015234	4	90162268	0.0006	A	0.052	1.53E-01	-	-	
RS10516570	4	112478170	0.001	G	0.022	5.72E-01	-	-	
RS17051353	4	122361659	0.0003	A	-0.067	2.65E-01	-	+	
RS13110000	4	123578060	0.0007	C	0.051	3.11E-01	-	-	
RS10440412	4	126734051	0.0006	T	-0.075	9.88E-02	-	+	
RS10017061	4	130788112	0.000027	A	-0.117	5.24E-01	-	+	
RS4487360	4	130790570	0.000031	T	-0.117	5.24E-01	-	+	
RS1517955	4	137912755	0.0001	T	-0.007	8.36E-01	-	+	
RS1319034	4	154966332	0.0007	C	-0.025	5.21E-01	-	+	
RS17372382	4	154968120	0.0007	G	-0.040	2.64E-01	-	+	
RS2611215	4	166574267	0.0006	A	0.063	2.98E-01	-	-	
RS2611212	4	166574651	0.0004	A	0.087	1.98E-01	-	-	
RS17688688	4	166592304	0.0005	A	0.049	5.52E-01	-	-	
RS1976543	4	170052646	0.0008	T	-0.070	6.08E-02	-	+	SH3RF1
RS2660432	4	170075171	0.0004	T	-0.067	7.55E-02	-	+	SH3RF1
RS10004048	4	170075273	0.0006	T	-0.068	7.16E-02	-	+	SH3RF1
RS11133119	4	176820049	0.0004	C	-0.028	4.34E-01	+	+	GPM6A
RS6827227	4	178755843	0.001	T	0.016	6.46E-01	-	-	LOC285501
RS12188301	5	1847639	0.0009	A	-0.033	7.90E-01	-	+	
RS1370978	5	10826267	0.0009	T	-0.022	6.12E-01	-	+	
RS16894002	5	24817630	0.0003	G	-0.024	8.19E-01	-	+	
RS10078309	5	24826395	0.0009	C	-0.019	8.58E-01	-	+	
RS10070340	5	36641769	0.0009	A	0.041	3.05E-01	-	-	SLC1A3
RS2124948	5	52928392	0.0005	T	-0.011	7.29E-01	+	+	NDUFS4
RS12517465	5	52942938	0.0005	A	-0.011	7.28E-01	+	+	NDUFS4
RS2290697	5	52978722	0.0007	T	-0.010	7.54E-01	+	+	NDUFS4
RS7730112	5	77251788	0.0005	A	0.045	4.82E-01	+	-	
RS16878218	5	80212435	0.0004	G	-0.009	8.57E-01	+	+	
RS2369629	5	98524496	0.0007	T	-0.008	8.12E-01	+	+	
RS989983	5	125034613	0.0003	A	0.004	9.31E-01	+	-	
RS245047	5	149327973	0.0003	T	-0.023	5.25E-01	-	+	
RS7731137	5	154005654	0.0006	T	-0.004	9.53E-01	-	+	
RS6895949	5	163273413	0.0005	A	0.062	2.52E-01	-	-	
RS1421862	5	163276790	0.0007	G	0.049	2.52E-01	-	-	
RS10060591	5	163293601	0.0001	T	0.058	4.11E-01	-	-	
RS11749716	5	165106225	0.0009	T	0.113	3.26E-02	-	-	
RS4701077	5	178604377	0.0002	T	0.013	8.65E-01	-	-	ADAMTS2
RS2170616	6	2557509	0.0006	T	-0.020	7.32E-01	-	+	
RS4959684	6	2589139	0.0007	T	-0.015	6.91E-01	+	+	
RS126646420	6	6282943	0.0007	G	0.015	7.30E-01	+	-	F13A1
RS9296672	6	13425532	0.0008	T	0.073	7.65E-02	+	-	GFOD1
RS2876366	6	14577131	0.0001	A	-0.050	3.51E-01	-	+	
RS9476596	6	14582008	0.0001	C	-0.051	3.60E-01	-	+	
RS1259065	6	15001506	0.0008	C	-0.033	3.21E-01	+	+	

RS4645427	6	18531115	0.0004	A	-0.018	6.30E-01	-	+	
RS4716289	6	18582886	0.0006	A	0.029	4.44E-01	+	-	
RS11751260	6	21959437	0.0002	C	0.044	2.82E-01	-	-	LINC00340
RS13212670	6	21969495	0.0009	T	0.010	7.90E-01	+	-	LINC00340
RS2534678	6	31463963	0.0003	T	0.041	4.37E-01	-	-	
RS2534657	6	31472459	0.0006	T	0.043	4.14E-01	-	-	MICB
RS2854028	6	33179689	0.0005	T	0.017	6.67E-01	-	-	RING1
RS2237093	6	36035354	0.0006	T	0.022	6.79E-01	-	-	MAPK14
RS9380546	6	36060240	0.0008	A	0.026	6.43E-01	-	-	MAPK14
RS4395718	6	36215693	0.0009	A	-0.006	8.84E-01	+	+	PNPLA1
RS12200371	6	38446634	0.0003	G	-0.015	8.03E-01	-	+	BTBD9
RS6458085	6	38884441	0.0007	A	-0.003	9.29E-01	-	+	LOC100131047
RS1964743	6	83445429	0.0008	A	0.106	1.55E-03	+	-	
RS7755798	6	109637154	0.0008	T	-0.002	9.60E-01	-	+	
RS1358771	6	132451644	0.001	G	0.027	4.93E-01	+	-	
RS6570330	6	139632859	0.0001	A	0.020	5.83E-01	+	-	
RS10946113	6	158584691	0.0005	A	0.069	5.52E-01	-	-	SERAC1
RS9365947	6	158588702	0.0005	T	0.106	2.21E-01	-	-	SERAC1
RS9348087	6	158598474	0.0005	T	0.106	2.15E-01	-	-	GTF2H5
RS9348153	6	158643526	0.0007	T	0.135	2.51E-01	-	-	
RS9348215	6	158685709	0.0009	T	0.065	1.78E-01	-	-	
RS10155975	7	13493700	0.0004	T	0.027	6.55E-01	+	-	
RS10242586	7	13497326	0.0002	T	0.039	5.12E-01	+	-	
RS4721415	7	15236132	0.0005	A	0.018	7.55E-01	-	-	
RS7792372	7	31213561	0.0005	C	-0.034	6.23E-01	-	+	
RS7803708	7	51148028	0.001	G	0.023	6.40E-01	-	-	COBL
RS10488323	7	52655888	0.0006	C	-0.017	7.56E-01	+	+	
RS10282659	7	81279925	0.0003	T	-0.014	7.43E-01	-	+	
RS10242168	7	81279976	0.0003	G	-0.016	7.18E-01	-	+	
RS258704	7	81762176	0.0002	C	-0.042	2.84E-01	-	+	CACNA2D1
RS10954664	7	81775555	0.0002	C	0.016	6.36E-01	+	-	CACNA2D1
RS3808267	7	90595848	0.0005	G	-0.038	3.47E-01	-	+	CDK14
RS1527680	7	94534886	0.0001	G	-0.071	4.23E-01	-	+	
RS17157128	7	103538333	0.0005	G	0.016	8.11E-01	-	-	RELN
RS10277802	7	103562551	0.001	A	-0.117	4.50E-01	-	+	RELN
RS284395	7	121885177	0.0007	A	-0.010	8.13E-01	-	+	
RS284391	7	121890781	0.0007	A	-0.010	8.17E-01	-	+	
RS4726603	7	139801222	0.0004	T	-0.003	9.71E-01	-	+	JHDM1D
RS1062277	7	139801777	0.0004	G	-0.002	9.81E-01	-	+	JHDM1D
RS11486906	7	139809574	0.0004	C	-0.003	9.71E-01	-	+	JHDM1D
RS12539339	7	140097554	0.0009	G	-0.074	4.15E-01	+	+	SLC37A3
RS855679	7	149478321	0.0008	C	0.015	8.06E-01	-	-	SSPO
RS7776495	7	154077301	0.0009	T	-0.010	7.87E-01	+	+	DPP6
RS1420823	8	5225481	0.0006	C	-0.014	6.93E-01	-	+	
RS7813625	8	27159459	0.0004	C	-0.018	7.92E-01	+	+	TRIM35
RS327329	8	31853498	0.0009	C	0.065	2.21E-01	+	-	NRG1
RS1462875	8	31860194	0.0005	A	0.048	2.12E-01	+	-	NRG1
RS10958713	8	42180716	0.0003	T	0.027	4.66E-01	-	-	IKBKB
RS1608806	8	83729106	0.0008	C	-0.080	1.33E-01	+	+	
RS2449529	8	98785523	0.0001	G	-0.049	4.42E-01	-	+	
RS6470446	8	127504653	0.0005	C	-0.010	8.97E-01	+	+	
RS1339287	9	8233804	0.0008	T	-0.019	6.10E-01	+	+	
RS1768575	9	8235513	0.001	A	-0.023	6.29E-01	+	+	
RS1341740	9	15850604	0.001	T	-0.026	7.92E-01	-	+	CCDC171
RS1359715	9	78354076	0.0007	T	0.003	9.56E-01	-	-	
RS155531	9	82535584	0.0003	C	0.047	2.13E-01	+	-	
RS267574	9	82535883	0.0009	A	0.042	2.64E-01	+	-	
RS3739809	9	82941434	0.0004	G	-0.089	8.93E-02	+	+	
RS11138635	9	82987698	0.0004	G	-0.035	3.95E-01	+	+	
RS3927559	9	83726045	0.0009	T	-0.003	9.49E-01	-	+	
RS10980551	9	113504910	0.001	G	0.002	9.64E-01	+	-	MUSK
RS10121207	9	119990164	0.0001	T	-0.039	2.69E-01	-	+	ASTN2
RS710074	9	133967295	0.0005	C	-0.019	8.00E-01	+	+	LAMC3
RS1320077	10	1618731	0.0001	A	-0.025	4.84E-01	-	+	ADARB2
RS1901633	10	4810561	0.000014	G	0.013	7.37E-01	-	-	
RS3123078	10	51524971	0.0003	C	-0.016	6.09E-01	-	+	
RS1099394	10	51549496	0.0006	T	-0.009	8.64E-01	-	+	

RS11634827	15	54513878	0.0007	G	-0.044	4.27E-01	-	+	<i>UNC13C</i>
RS12101550	15	92857342	0.0009	G	-0.068	2.34E-01	+	+	
RS8043535	15	97392522	0.0006	C	0.019	6.02E-01	-	-	
RS8042199	15	97392553	0.0007	G	0.019	6.01E-01	-	-	
RS1703794	15	99613173	0.000035	C	0.006	8.87E-01	+	-	
RS1670200	15	99613245	0.0002	C	0.042	2.34E-01	-	-	
RS6497441	16	9829848	0.0009	T	-0.022	7.86E-01	+	+	
RS9925256	16	52473263	0.0009	G	-0.017	6.39E-01	-	+	<i>TOX3</i>
RS2550364	16	58228701	0.0007	C	-0.031	3.60E-01	-	+	<i>CSNK2A2</i>
RS12599067	16	76777664	0.0007	A	-0.005	9.32E-01	-	+	
RS2966099	16	81550448	0.0007	C	0.021	7.01E-01	-	-	<i>CMIP</i>
RS9891235	17	31836993	0.0005	C	-0.015	7.96E-01	+	+	<i>ASIC2</i>
RS4791201	17	63314560	0.0005	G	-0.001	9.91E-01	-	+	
RS8068707	17	63315996	0.0004	C	0.024	6.05E-01	-	-	
RS10438701	17	71395173	0.0009	G	-0.027	7.35E-01	+	+	<i>SDK2</i>
RS6565593	17	79515075	0.0005	A	0.025	4.73E-01	-	-	<i>C17orf70</i>
RS3830068	17	79622899	0.0008	C	0.051	1.87E-01	-	-	<i>PDE6G</i>
RS6506569	18	8275857	8.40E-06	C	-0.050	1.43E-01	+	+	<i>PTPRM</i>
RS11080567	18	12312075	0.0002	T	0.053	5.04E-01	-	-	<i>TUBB6</i>
RS12607321	18	12316779	0.0001	C	0.053	5.02E-01	-	-	<i>TUBB6</i>
RS7231304	18	12350505	0.0004	C	0.036	6.02E-01	-	-	<i>AFG3L2</i>
RS1945162	18	22166762	0.0004	T	0.025	5.93E-01	+	-	
RS1945166	18	22169993	0.0004	C	0.025	5.81E-01	+	-	
RS12608350	18	27828310	0.0002	T	-0.009	8.03E-01	+	+	
RS4799816	18	33384924	0.0003	C	-0.060	3.48E-01	+	+	
RS1942240	18	33387429	0.0005	C	-0.057	3.54E-01	+	+	
RS10502880	18	44770746	0.0005	C	-0.021	5.42E-01	-	+	<i>SKOR2</i>
RS12327160	18	73731308	0.0009	G	-0.040	3.26E-01	-	+	
RS1542951	18	75591259	0.000075	C	0.030	6.96E-01	+	-	
RS731723	19	12588119	0.0004	C	-0.042	5.81E-01	+	+	<i>ZNF709</i>
RS6113161	20	2171649	0.0005	G	0.112	1.72E-02	-	-	
RS6082438	20	2204811	0.00009	T	-0.005	8.86E-01	-	+	
RS6116308	20	4295353	0.0006	A	-0.054	3.07E-01	-	+	
RS2148815	20	6363480	0.001	T	-0.009	8.07E-01	+	+	
RS6085681	20	6770690	0.0009	A	-0.016	6.54E-01	+	+	
RS2650972	20	6783274	0.000032	T	0.007	8.49E-01	-	-	
RS1545	20	10386013	0.0009	A	-0.025	6.37E-01	-	+	<i>MKKS</i>
RS16991547	20	10394046	0.0009	A	-0.028	5.96E-01	-	+	<i>MKKS</i>
RS6133927	20	10406156	0.0009	G	-0.029	5.87E-01	-	+	<i>MKKS</i>
RS852105	20	17154897	0.0009	T	0.038	7.36E-01	-	-	
RS726256	20	17456843	0.0008	T	-0.004	8.96E-01	+	+	<i>PCSK2</i>
RS6080714	20	17472515	0.0002	G	-0.006	8.63E-01	-	+	
RS6028910	20	38784641	0.001	G	0.040	6.30E-01	+	-	
RS400420	20	55470340	0.0007	A	0.016	6.60E-01	-	-	
RS2249634	20	55470625	0.0004	G	0.038	2.81E-01	-	-	
RS1276434	20	55479307	0.0003	G	0.005	8.88E-01	-	-	
RS6064463	20	55480277	0.000041	C	-0.010	7.82E-01	-	+	
RS6027736	20	59260773	0.0008	C	-0.084	1.04E-01	+	+	
RS17802507	20	59269198	0.001	C	-0.081	1.19E-01	+	+	
RS11700217	20	61407407	0.001	A	-0.053	4.09E-01	-	+	<i>LOC100652730</i>
RS150760	21	27808458	0.0009	A	-0.005	8.84E-01	-	+	<i>LOC100996571</i>
RS2836544	21	39963124	0.0009	A	0.047	2.11E-01	-	-	<i>ERG</i>
RS2836565	21	39976701	0.0003	A	0.018	6.26E-01	-	-	<i>ERG</i>
RS724055	22	30675923	0.0003	A	0.006	8.62E-01	-	-	

Supplementary Table 9. DAS28 results for all SNPs with P<0.0001 in a genome-wide study of methotrexate response in European juvenile idiopathic arthritis patients (Cobb et al.)

Effect direction is in relation to effect allele: + indicates improvement in DAS28 score/response, - indicates increase in DAS score/non-response.

Marker	Chr	Position	Cobb et al. P-value	Effect Allele	DAS28		Effect Direction		gene
					β	P-value	Cobb et al.	This Study	
RS951437	1	163033511	6.45x10-4	T	-0.027	6.27E-01	-	+	
RS951438	1	163033537	6.45x10-4	T	-0.026	6.36E-01	-	+	
RS2661319	1	163039777	7.71x10-4	T	0.045	3.71E-01	+	-	RGS4
RS4657400	1	165103961	4.65x10-5	C	0.057	3.17E-01	-	-	
RS2972472	3	115447624	8.52x10-4	C	-0.052	2.44E-01	+	+	
RS11707482	3	126099612	3.63x10-4	A	0.038	3.35E-01	-	-	LOC100506907
RS9864977	3	126101047	4.89x10-4	C	0.037	3.37E-01	-	-	LOC100506907
RS2270813	5	157164889	7.25x10-5	T	0.017	6.35E-01	+	-	THG1L
RS2270812	5	157164962	7.25x10-5	T	0.021	5.73E-01	+	-	THG1L
RS300195	5	162698920	7.21x10-4	T	0.014	9.06E-01	-	-	
RS1465221	7	77764253	7.34x10-4	A	0.021	7.17E-01	+	-	MAGI2
RS3917558	7	94932904	5.35x10-4	C	0.099	2.78E-01	-	-	PON1
RS3917556	7	94933189	7.96x10-4	C	0.069	5.77E-01	-	-	PON1
RS3917551	7	94934455	8.07x10-4	A	0.069	5.77E-01	-	-	PON1
RS3917548	7	94935905	7.96x10-4	G	0.052	6.27E-01	-	-	PON1
RS3917541	7	94937624	7.96x10-4	A	0.055	5.97E-01	-	-	PON1
RS2158155	7	94938176	7.96x10-4	A	0.077	5.06E-01	-	-	PON1
RS2299257	7	94942765	5.35x10-4	C	-0.013	7.24E-01	-	+	PON1
RS854556	7	94944923	9.11x10-4	T	-0.037	3.04E-01	+	+	PON1
RS854557	7	94945215	9.11x10-4	G	-0.036	3.23E-01	+	+	PON1
RS2301711	7	94945659	6.79x10-4	C	0.052	5.88E-01	-	-	PON1
RS854559	7	94945872	7.40x10-4	A	-0.038	3.02E-01	+	+	PON1
RS854561	7	94947017	9.11x10-4	T	-0.038	3.02E-01	+	+	PON1
RS854562	7	94947969	8.48x10-5	T	-0.026	4.84E-01	+	+	PON1
RS854563	7	94948009	9.11x10-4	A	-0.038	3.02E-01	+	+	PON1
RS3917493	7	94948028	7.96x10-4	C	0.085	4.16E-01	-	-	PON1
RS17611963	7	122520343	9.00x10-4	T	-0.065	4.25E-01	-	+	CADPS2
RS16939230	8	76939927	7.27x10-5	G	0.085	2.31E-01	-	-	
RS11988715	8	76944293	4.51x10-4	T	0.069	2.52E-01	-	-	
RS13274868	8	82921787	2.48x10-4	T	-0.022	5.77E-01	-	+	
RS4529421	8	82921979	5.73x10-4	G	-0.065	6.97E-02	-	+	
RS998249	8	82961957	4.72x10-4	T	-0.018	6.19E-01	-	+	
RS1576733	9	84141525	5.20x10-5	C	0.044	2.28E-01	-	-	
RS703979	10	80944095	7.69x10-4	T	0.129	1.10E-04	-	-	ZMIZ1
RS703970	10	80953136	8.26x10-5	A	0.124	1.77E-04	-	-	ZMIZ1
RS697237	10	80954686	7.06x10-4	A	0.135	2.88E-03	-	-	ZMIZ1
RS2802371	10	80961519	1.41x10-5	C	0.084	1.06E-02	-	-	ZMIZ1
RS1250576	10	80964796	9.28x10-5	C	0.107	1.90E-03	-	-	ZMIZ1
RS942796	10	80967220	3.14x10-4	T	0.097	3.98E-03	-	-	ZMIZ1
RS1250582	10	80973447	2.09x10-5	T	0.083	1.16E-02	-	-	ZMIZ1
RS1250591	10	80985374	7.29x10-5	A	-0.073	3.00E-02	+	+	ZMIZ1
RS17680055	11	99778206	6.17x10-4	G	0.079	5.09E-02	-	-	CNTN5
RS11609579	12	101843240	2.62x10-4	G	0.101	2.20E-02	-	-	
RS11110810	12	101856465	5.08x10-4	T	0.105	2.77E-02	-	-	
RS595775	13	101840684	3.46x10-4	T	-0.059	9.30E-02	-	+	NALCN
RS1896195	15	26770557	8.98x10-4	C	-0.003	9.38E-01	+	+	
RS4906679	15	26814773	2.45x10-4	C	0.014	7.02E-01	+	-	GABRB3
RS4906680	15	26816588	3.33x10-4	A	0.008	8.19E-01	+	-	GABRB3
RS882898	20	60320706	8.51x10-4	A	0.060	1.40E-01	+	-	CDH4
RS11699916	20	60326201	1.84x10-4	A	0.085	2.54E-02	+	-	CDH4

Supplementary Table 11. Annotation of the most highly associated regions at $P < 1e-5$ for each of the 4 traits analysed genome-wide

Genes: with SNP or supporting SNPs with $P < 5e-5$ located within gene

Nearby Genes: all genes less than 20kb from the start and stop of the hit region

Chromatin interactions: show the genes with most significant long-range chromatin interactions in GM12878 with the 25 top loci

Number of SNPs in Score: shows the number of SNPs in the region used to create a regional genetic score predicting response to MTX

Number of SNPs in Searle shows the number of SNPs in the region used to create a regional genetic score predicting response to MTX.

Correlations: shows the correlations between the regional genetic score and the scores for the traits in the previous column (separated by comma)

Supplementary Table 12. Phase 1 results for the most significant regions from an analysis of EULAR responders (Good and Moderate) versus non-responders.
 Regions are shown if they included one SNP with $P < 1 \times 10^{-5}$ and at least one other SNP within 200kb with $P < 5 \times 10^{-5}$

Marker	Chr	Position	Non-responders	Responders	Effect Allele	Odds Ratio for non-response	P
RS10889647:67154496:T:A	1	67154496	413	831	A	1.49	4.82E-05
RS1408852:67155328:T:C	1	67155328	413	831	C	1.49	4.58E-05
RS682896:67186062:T:C	1	67186062	413	831	T	1.49	3.77E-05
RS269072:112593217:T:C	1	112593217	413	831	C	1.43	4.99E-05
RS655856:112594445:G:A	1	112594445	413	831	A	1.43	4.24E-05
RS543966:112594930:C:T	1	112594930	413	831	T	1.43	4.98E-05
RS269074:112596703:A:C	1	112596703	413	831	C	1.43	4.93E-05
RS1867402:112597212:T:C	1	112597212	413	831	C	1.43	4.91E-05
RS269076:112597282:C:G	1	112597282	413	831	G	1.43	4.91E-05
RS269079:112597532:A:G	1	112597532	413	831	G	1.43	4.99E-05
RS7584342:166288314:C:T	2	166288314	413	831	T	1.63	4.22E-05
RS6758348:166292513:A:C	2	166292513	413	831	C	1.64	3.60E-05
RS420914:4275016:A:G	5	4275016	413	831	A	1.77	1.22E-05
RS62343132:4275018:A:G	5	4275018	413	831	A	1.77	1.22E-05
RS63749549:4275020:A:G	5	4275020	413	831	A	1.77	1.22E-05
RS62343133:4275022:A:G	5	4275022	413	831	A	1.77	1.22E-05
RS10042800:4275024:A:G	5	4275024	413	831	A	1.77	1.22E-05
RS7703981:151944065:A:G	5	151944065	413	831	G	1.93	4.61E-05
RS17113408:151945295:A:T	5	151945295	413	831	T	1.93	4.46E-05
RS6875259:151946335:G:T	5	151946335	413	831	T	1.93	4.47E-05
RS58664268:151947234:G:A	5	151947234	413	831	A	1.93	4.46E-05
RS17113421:151947300:T:C	5	151947300	413	831	C	1.93	4.48E-05
RS6891765:151947696:G:A	5	151947696	413	831	A	1.93	4.67E-05
RS55970355:151948482:A:G	5	151948482	413	831	G	1.93	4.49E-05
RS6867859:151950297:G:T	5	151950297	413	831	T	1.92	4.76E-05
RS56091795:151954561:G:A	5	151954561	413	831	A	1.96	4.24E-05
RS61608756:151958695:G:C	5	151958695	413	831	C	1.92	4.99E-05
RS62395569:151959418:G:A	5	151959418	413	831	A	1.92	4.93E-05
RS79641272:151970619:G:C	5	151970619	413	831	C	1.96	3.51E-05
RS62395602:152002839:C:T	5	152002839	413	831	T	2.01	3.97E-05
RS17113527:152017153:A:T	5	152017153	413	831	T	1.95	4.55E-05
RS7730407:152028739:T:C	5	152028739	413	831	C	1.95	4.49E-05
RS61494452:152032374:T:C	5	152032374	413	831	C	1.95	4.49E-05
RS11953908:152033079:G:A	5	152033079	413	831	A	1.95	4.52E-05
RS146321269:152035133:C:T	5	152035133	413	831	T	1.81	3.10E-05
RS6877248:152043215:T:C	5	152043215	413	831	C	1.95	4.97E-05
RS62398677:152044579:T:C	5	152044579	413	831	C	1.95	4.72E-05
RS55641807:152047538:G:A	5	152047538	413	831	A	1.95	4.66E-05
RS56214789:152047682:G:A	5	152047682	413	831	A	1.95	4.67E-05
RS430962:152052316:C:T	5	152052316	413	831	T	1.99	3.25E-05
RS2390595:21915464:G:A	7	21915464	413	831	A	0.68	4.24E-05
RS13308113:21917360:G:A	7	21917360	413	831	G	0.67	2.31E-05
RS10227946:78315218:G:A	7	78315218	413	831	A	0.66	2.21E-05
RS10255247:78389781:C:T	7	78389781	413	831	T	0.67	4.70E-05
RS37876:78431095:C:G	7	78431095	413	831	G	0.68	4.65E-05
RS37880:78434236:T:G	7	78434236	413	831	G	0.68	4.91E-05
RS246460:78441198:T:C	7	78441198	413	831	C	0.67	2.95E-05
RS246462:78443174:A:G	7	78443174	413	831	G	0.67	2.94E-05
RS13268737:22101593:T:C	8	22101593	413	831	C	0.65	2.67E-05
RS13249656:22113565:G:T	8	22113565	413	831	T	0.65	3.25E-05
RS12549719:22116085:A:G	8	22116085	413	831	G	0.65	3.73E-05
RS2585139:143808175:C:G	8	143808175	466	926	G	0.72	4.69E-05
RS7010768:143825951:T:G	8	143825951	466	926	T	0.71	4.65E-05
RS4567164:100206602:C:G	9	100206602	413	831	C	0.40	2.45E-06
RS6415827:100244171:G:A	9	100244171	413	831	G	0.55	4.92E-05
RS4742695:100256460:A:C	9	100256460	413	831	A	0.55	4.71E-05
RS41302651:130167338:C:T	9	130167338	466	926	T	1.46	5.65E-06
RS3824413:130167390:C:T	9	130167390	466	926	T	1.45	5.90E-06
RS3802363:130167569:T:C	9	130167569	466	926	C	1.45	5.86E-06

RS10987637:130168326:C:T	9	130168326	466	926	T	1.43	1.76E-05
RS72767909:130168873:C:T	9	130168873	466	926	T	1.45	6.05E-06
RS4075850:130169301:G:A	9	130169301	466	926	A	1.45	6.03E-06
RS6635:130169874:A:G	9	130169874	466	926	G	1.45	6.04E-06
RS3088163:130170000:A:T	9	130170000	466	926	T	1.45	6.02E-06
RS10819288:130170311:T:G	9	130170311	466	926	G	1.46	5.70E-06
RS62579723:130170806:G:A	9	130170806	466	926	A	1.45	6.01E-06
RS62579724:130170831:G:A	9	130170831	466	926	A	1.45	6.02E-06
RS142175068:130170950:T:C	9	130170950	466	926	C	1.45	6.01E-06
RS12379702:130172055:T:C	9	130172055	466	926	C	1.45	5.99E-06
RS55976691:130172469:C:T	9	130172469	466	926	T	1.45	5.98E-06
RS7866114:130173253:A:G	9	130173253	466	926	G	1.44	9.23E-06
RS10987641:130173451:G:A	9	130173451	466	926	A	1.45	5.92E-06
RS7047760:130175096:G:A	9	130175096	466	926	A	1.46	5.69E-06
RS10987644:130175933:C:T	9	130175933	466	926	T	1.46	5.85E-06
RS7035547:130178912:T:C	9	130178912	466	926	C	1.43	1.51E-05
RS62579727:130179808:A:G	9	130179808	466	926	G	1.43	1.56E-05
RS4074145:130180404:A:G	9	130180404	466	926	G	1.43	1.64E-05
RS17464948:130181886:T:C	9	130181886	466	926	T	0.69	1.72E-05
RS62579728:130182596:T:G	9	130182596	466	926	T	0.69	1.78E-05
RS6415844:130183114:T:C	9	130183114	466	926	T	0.69	1.44E-05
RS4316239:130183486:G:C	9	130183486	466	926	G	0.69	1.75E-05
RS10987648:130183790:T:C	9	130183790	466	926	T	0.69	1.45E-05
RS3924308:130185385:C:A	9	130185385	466	926	C	0.68	8.87E-06
RS7470971:130185708:A:T	9	130185708	466	926	A	0.68	1.06E-05
RS7020736:130187866:T:G	9	130187866	466	926	G	1.44	1.35E-05
RS62586845:130188796:G:A	9	130188796	466	926	A	1.44	1.27E-05
RS3923308:130197225:G:A	9	130197225	466	926	A	1.44	1.11E-05
RS10987652:130200577:T:C	9	130200577	466	926	T	1.44	1.07E-05
RS10987653:130201107:T:C	9	130201107	466	926	C	1.44	1.07E-05
RS10987654:130201206:C:T	9	130201206	466	926	T	1.44	1.07E-05
RS7869384:130201941:C:T	9	130201941	466	926	T	1.44	1.07E-05
RS7869873:130202302:C:T	9	130202302	466	926	T	1.44	1.07E-05
RS12380014:130204394:A:G	9	130204394	466	926	G	1.44	1.07E-05
RS2265816:130205517:C:T	9	130205517	466	926	T	1.44	1.07E-05
RS2248154:130206134:C:T	9	130206134	466	926	T	1.44	1.07E-05
RS2248025:130206762:C:T	9	130206762	466	926	T	1.44	1.07E-05
RS2247687:130209637:T:C	9	130209637	466	926	C	1.44	1.07E-05
RS2247682:130209700:A:C	9	130209700	466	926	C	1.44	1.07E-05
RS2491101:130215249:C:T	9	130215249	466	926	T	1.44	9.95E-06
RS2244331:130216120:G:T	9	130216120	466	926	T	1.45	9.18E-06
RS2244218:130216951:G:T	9	130216951	466	926	T	1.45	9.07E-06
RS2243509:130217050:C:G	9	130217050	466	926	G	1.45	9.15E-06
RS2798430:130220879:A:T	9	130220879	466	926	T	1.45	8.04E-06
RS2254164:130227079:T:A	9	130227079	466	926	A	1.45	8.09E-06
RS2253930:130228495:A:G	9	130228495	466	926	G	1.45	8.62E-06
RS2253898:130229262:A:G	9	130229262	466	926	G	1.45	8.62E-06
RS2253811:130229564:C:A	9	130229564	466	926	A	1.44	9.81E-06
RS2253806:130229652:A:G	9	130229652	466	926	A	0.71	4.18E-05
RS2253414:130232890:T:A	9	130232890	466	926	A	1.41	3.43E-05
RS2253411:130232909:G:C	9	130232909	466	926	C	1.41	3.43E-05
RS111988501:130233956:C:T	9	130233956	466	926	T	1.41	3.41E-05
RS62584994:130234594:G:A	9	130234594	466	926	A	1.47	1.04E-05
RS115721486:130234596:G:A	9	130234596	466	926	A	1.42	2.98E-05
RS2995822:130234634:A:G	9	130234634	466	926	G	1.42	2.36E-05
RS2250267:130236243:G:A	9	130236243	466	926	A	1.42	2.25E-05
RS2250184:130236589:C:G	9	130236589	466	926	G	1.42	2.95E-05
RS2250161:130237356:T:C	9	130237356	466	926	C	1.42	2.29E-05
RS2250021:130238122:T:C	9	130238122	466	926	C	1.42	2.28E-05
RS2250020:130238160:T:C	9	130238160	466	926	T	1.42	2.28E-05
RS2249936:130238645:C:G	9	130238645	466	926	G	1.42	2.25E-05
RS2249803:130239900:G:A	9	130239900	466	926	A	1.42	2.26E-05
RS1539568:130242109:C:T	9	130242109	466	926	T	1.42	2.25E-05

RS2246600:130243846:G:A	9	130243846	466	926	A	1.42	2.24E-05
RS7875862:130245545:G:C	9	130245545	466	926	C	1.42	2.24E-05
RS2246375:130245787:T:T	9	130245787	466	926	T	1.42	2.24E-05
RS62584996:130247355:G:T	9	130247355	466	926	T	1.42	2.27E-05
RS2243464:130248366:T:A	9	130248366	466	926	A	1.42	2.25E-05
RS2245677:130251512:G:A	9	130251512	466	926	A	1.44	1.20E-05
RS1547840:130252307:T:A	9	130252307	466	926	T	1.42	2.77E-05
RS1539564:130253931:A:G	9	130253931	466	926	G	1.42	2.35E-05
RS2249290:130255568:C:T	9	130255568	466	926	T	1.42	2.61E-05
RS2798429:130257191:G:A	9	130257191	466	926	A	1.42	2.72E-05
RS2249052:130258160:A:T	9	130258160	466	926	T	1.42	2.31E-05
RS2248725:130260788:C:T	9	130260788	466	926	T	1.43	2.00E-05
RS2488902:130261085:C:T	9	130261085	466	926	T	1.43	1.91E-05
RS62584998:130262434:G:T	9	130262434	466	926	T	1.42	2.38E-05
RS2245461:130266088:G:A	9	130266088	466	926	G	0.70	1.92E-05
RS2245445:130266399:G:A	9	130266399	466	926	G	0.70	2.88E-05
RS2244957:130271051:G:A	9	130271051	466	926	G	0.69	1.59E-05
RS2265814:130274290:T:G	9	130274290	466	926	T	0.71	4.36E-05
RS2254719:130282097:G:A	9	130282097	466	926	G	0.71	3.56E-05
RS7075325:3359961:G:A	10	3359961	466	926	A	0.71	3.91E-05
RS11595859:3360188:C:T	10	3360188	466	926	T	0.70	3.14E-05
RS12765037:3366559:T:G	10	3366559	466	926	G	0.70	3.67E-05
RS11594429:3368555:A:G	10	3368555	466	926	G	0.70	3.60E-05
RS1572539:3373163:G:C	10	3373163	466	926	C	0.71	4.02E-05
RS2297761:3377859:C:T	10	3377859	466	926	T	0.70	2.79E-05
RS12415414:3378151:T:C	10	3378151	466	926	C	0.71	4.37E-05
RS11597857:3378897:T:G	10	3378897	466	926	G	0.70	2.80E-05
RS11814386:3381890:C:T	10	3381890	466	926	T	0.70	4.21E-05
RS11251856:3381912:T:C	10	3381912	466	926	C	0.70	4.04E-05
RS11251857:3382156:A:G	10	3382156	466	926	G	0.70	3.57E-05
RS11251859:3382482:C:G	10	3382482	466	926	G	0.71	4.35E-05
RS34033143:3382723:T:G	10	3382723	466	926	G	0.70	4.12E-05
RS2924279:4863093:G:A	10	4863093	413	831	G	1.54	1.25E-05
RS2961620:4863351:C:T	10	4863351	413	831	C	1.54	1.03E-05
RS745290:30790264:T:C	10	30790264	466	926	C	1.48	2.02E-05
RS10763790:30791355:G:C	10	30791355	466	926	C	1.49	1.42E-05
RS728976:30792581:C:T	10	30792581	466	926	T	1.49	1.42E-05
RS11008075:30793299:C:G	10	30793299	466	926	G	1.49	1.16E-05
RS10763791:30794155:T:C	10	30794155	466	926	C	1.49	1.18E-05
RS57172677:30800604:T:C	10	30800604	466	926	C	1.48	2.16E-05
RS11008080:30802799:A:C	10	30802799	466	926	C	1.45	4.39E-05
RS882080:30804597:T:A	10	30804597	466	926	A	1.48	2.06E-05
RS2002695:30805480:A:G	10	30805480	466	926	G	1.48	2.12E-05
RS2009810:30806199:T:A	10	30806199	466	926	A	1.48	2.22E-05
RS12774393:30806833:G:C	10	30806833	466	926	C	1.48	2.35E-05
RS7296850:67338701:A:T	12	67338701	413	831	T	1.45	2.78E-05
RS6581724:67339018:A:G	12	67339018	413	831	G	1.45	3.03E-05
RS7966850:67340137:A:T	12	67340137	413	831	T	1.45	2.40E-05
RS7136625:67340896:T:C	12	67340896	413	831	C	1.52	2.20E-06
RS6581725:67350123:T:C	12	67350123	413	831	T	0.66	8.64E-06
RS1604843:67351176:A:G	12	67351176	413	831	A	0.66	9.42E-06
RS1354442:67351481:T:A	12	67351481	413	831	T	0.66	9.50E-06
RS10878540:67352669:C:T	12	67352669	413	831	C	0.66	9.67E-06
RS10878542:67356453:G:A	12	67356453	413	831	G	0.66	9.66E-06
RS4277193:67361657:G:A	12	67361657	413	831	G	0.66	9.73E-06
RS1604841:67362788:A:G	12	67362788	413	831	A	0.66	9.82E-06
RS2089133:67364152:T:C	12	67364152	413	831	T	0.66	9.89E-06
RS1117041:67364485:A:G	12	67364485	413	831	A	0.66	1.00E-05
RS1896092:108395223:C:T	12	108395223	413	831	C	1.62	3.70E-05
RS1896093:108395719:T:C	12	108395719	413	831	T	1.61	4.19E-05
RS1896096:108396894:C:T	12	108396894	413	831	C	1.61	4.16E-05
RS10861850:108399880:T:C	12	108399880	413	831	T	1.62	3.58E-05
RS714906:108401324:G:C	12	108401324	413	831	G	1.62	3.54E-05

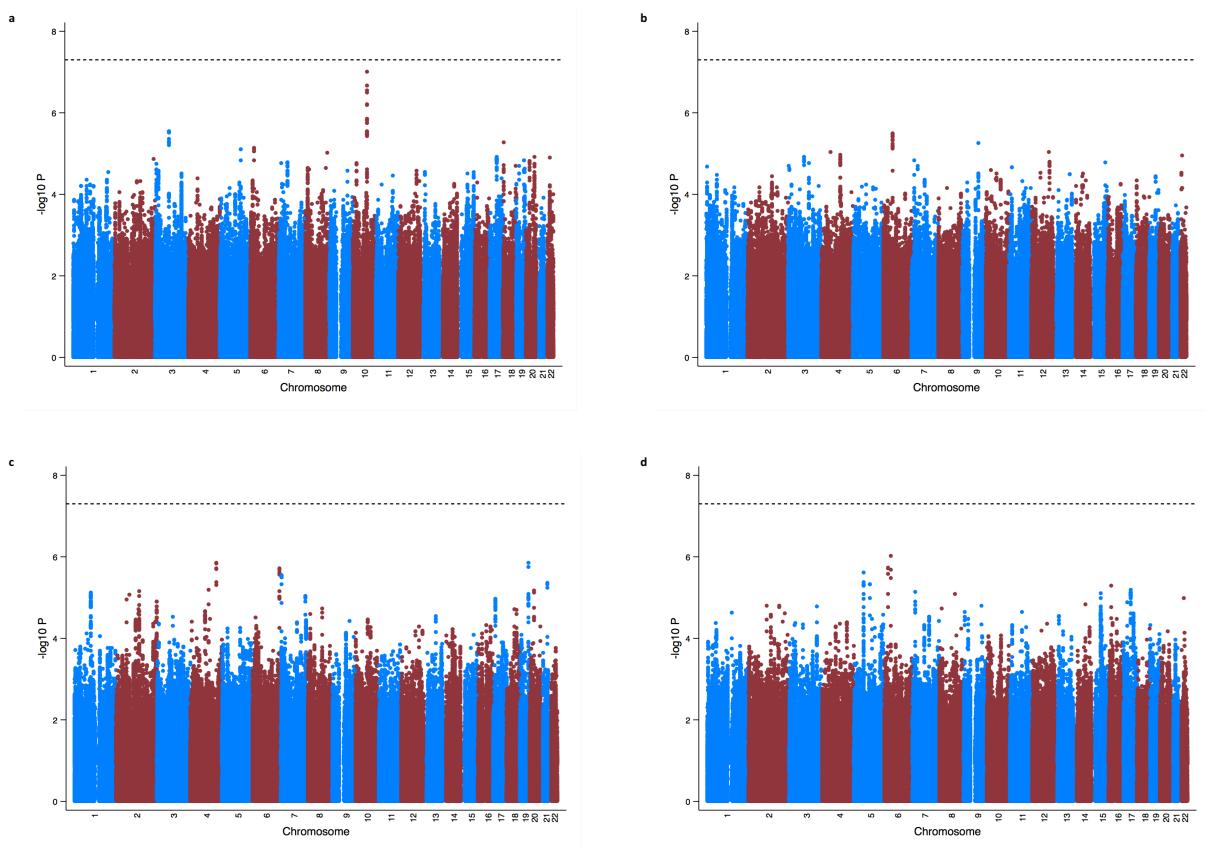
RS1896052:108402518:C:A	12	108402518	413	831	C	1.62	3.52E-05
RS6539400:108402874:C:A	12	108402874	413	831	C	1.62	3.50E-05
RS2194988:108403370:T:C	12	108403370	413	831	T	1.63	4.12E-05
RS4459358:108404076:A:T	12	108404076	413	831	A	1.62	3.42E-05
RS1896061:108408845:C:G	12	108408845	413	831	C	1.62	3.24E-05
RS1896062:108408861:T:A	12	108408861	413	831	T	1.62	3.69E-05
RS1896063:108408969:C:A	12	108408969	413	831	C	1.62	3.24E-05
RS1896065:108409623:T:G	12	108409623	413	831	T	1.62	3.68E-05
RS1896071:108410993:C:G	12	108410993	413	831	C	1.62	3.52E-05
RS1896080:108414313:C:T	12	108414313	413	831	C	1.62	3.64E-05
RS7974678:108417105:T:C	12	108417105	413	831	T	1.61	4.03E-05
RS7296801:108433529:G:C	12	108433529	413	831	G	1.61	4.53E-05
RS7305634:108465742:G:A	12	108465742	413	831	G	1.61	4.36E-05
RS4475966:108466021:T:C	12	108466021	413	831	T	1.61	4.35E-05
RS10746115:108475650:C:T	12	108475650	413	831	C	1.65	1.85E-05
RS10778607:108475893:G:T	12	108475893	413	831	G	1.64	2.40E-05
RS10778608:108476202:T:C	12	108476202	413	831	T	1.59	4.98E-05
RS1431977:3620717:G:T	17	3620717	466	926	T	0.71	3.43E-05
RS1977020:3622508:C:T	17	3622508	466	926	T	1.44	2.24E-05
RS16953429:3626816:G:A	17	3626816	466	926	A	1.43	3.68E-05
RS12943844:3631620:G:C	17	3631620	466	926	G	1.48	8.26E-06
RS55661368:19427601:C:A	17	19427601	413	831	A	0.69	3.10E-05
RS2440164:19428610:A:G	17	19428610	413	831	G	0.69	2.61E-05
RS2440165:19428719:T:C	17	19428719	413	831	C	0.69	2.61E-05
RS11870808:19429379:G:C	17	19429379	413	831	C	0.69	2.28E-05
RS8071709:19429790:A:C	17	19429790	413	831	C	0.69	4.27E-05
RS2453578:19430645:T:C	17	19430645	413	831	C	0.69	3.45E-05
RS111374932:19431959:T:C	17	19431959	413	831	C	0.69	2.48E-05
RS11871125:19432393:C:T	17	19432393	413	831	T	0.69	2.48E-05
RS2252281:19437187:T:C	17	19437187	413	831	C	0.69	3.55E-05
RS2453580:19438321:T:C	17	19438321	413	831	C	0.70	4.14E-05
RS2453581:19438560:C:T	17	19438560	413	831	T	0.69	2.81E-05
RS2453582:19439066:C:T	17	19439066	413	831	T	0.69	3.10E-05
RS894680:19440538:G:A	17	19440538	413	831	A	0.69	2.62E-05
RS2453583:19442036:A:T	17	19442036	413	831	T	0.68	1.87E-05
RS2453584:19443445:G:C	17	19443445	413	831	C	0.67	1.20E-05
RS4817650:16480898:C:T	21	16480898	413	831	T	0.64	8.26E-07
RS2823061:16481665:G:A	21	16481665	413	831	A	0.66	2.52E-06
RS4816486:16482620:A:G	21	16482620	413	831	G	0.66	3.07E-06
RS2823062:16482643:T:G	21	16482643	413	831	G	0.66	3.50E-06
RS9978683:16483454:G:A	21	16483454	413	831	A	0.66	4.33E-06
RS7282412:16484651:T:A	21	16484651	413	831	A	0.66	3.71E-06
RS2823065:16485897:C:T	21	16485897	413	831	T	0.66	7.61E-06
RS2823066:16486315:G:A	21	16486315	413	831	A	0.66	1.06E-05
RS2026849:16486626:G:A	21	16486626	413	831	A	0.66	1.30E-05

Supplementary Table 13. Phase 1 results for the most significant regions from an analysis of EULAR Good responders versus non-responders.

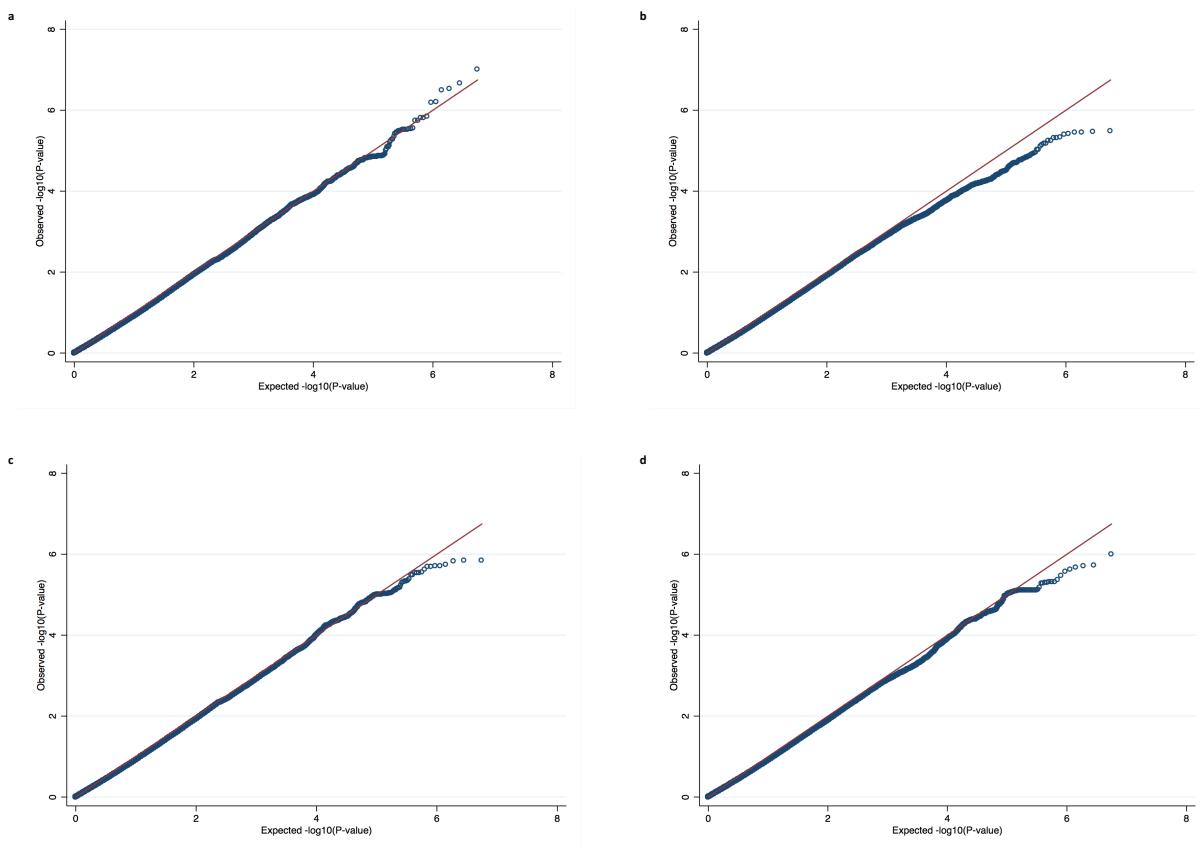
Regions are shown if they included one SNP with $P < 1 \times 10^{-5}$ and at least one other SNP within 200kb with $P < 5 \times 10^{-5}$

Marker	Chr	Position	Non-responders	Good Responders	Effect Allele	Odds Ratio for non-response	P
RS79944340:76866742:G:A	1	76866742	413	383	A	2.35	3.85E-06
RS11577449:76869325:T:A	1	76869325	413	383	A	2.34	4.00E-06
RS61771525:76892302:A:G	1	76892302	413	383	G	1.82	3.05E-05
RS6577247:101865870:G:T	1	101865870	413	383	G	0.37	2.87E-05
RS11164191:101866707:C:T	1	101866707	413	383	C	0.39	4.77E-05
RS4908139:101866905:G:C	1	101866905	413	383	G	0.39	4.47E-05
RS10874488:101867800:G:A	1	101867800	413	383	G	0.37	2.81E-05
RS7540539:101869322:T:A	1	101869322	413	383	T	0.37	2.79E-05
RS12128264:203575060:T:G	1	203575060	413	383	T	0.63	1.54E-05
RS12121279:203576156:G:T	1	203576156	413	383	G	0.64	2.11E-05
RS12131388:203577939:T:C	1	203577939	413	383	T	0.63	1.78E-05
RS12125553:203580111:G:T	1	203580111	413	383	G	0.64	1.90E-05
RS1970963:203586060:T:A	1	203586060	413	383	T	0.64	3.14E-05
RS7568567:151786203:C:G	2	151786203	413	383	G	1.52	4.91E-05
RS1118980:151839884:G:T	2	151839884	413	383	G	0.64	3.22E-05
RS13026509:151853097:G:C	2	151853097	413	383	G	0.64	2.52E-05
RS12987768:151872127:C:T	2	151872127	413	383	C	0.64	2.03E-05
RS12990477:151885001:G:A	2	151885001	413	383	G	0.64	3.90E-05
RS1546485:14533006:A:T	8	14533006	413	383	A	0.64	1.07E-05
RS28842205:14545161:C:T	8	14545161	413	383	C	1.52	4.62E-05
RS1510454:14553223:A:T	8	14553223	413	383	T	0.65	2.35E-05
RS6999437:14554875:T:C	8	14554875	413	383	T	1.53	3.80E-05
RS6995277:14554878:A:C	8	14554878	413	383	A	1.53	3.80E-05
RS7017742:14554992:C:T	8	14554992	413	383	C	1.53	3.81E-05
RS17321361:14555348:A:T	8	14555348	413	383	A	1.52	4.32E-05
RS2247039:14659604:C:G	8	14659604	413	383	C	0.65	1.81E-05
RS28843818:14661422:T:C	8	14661422	413	383	C	1.54	2.62E-05
RS28798118:14661423:G:C	8	14661423	413	383	C	1.54	2.62E-05
RS28877698:14661444:C:A	8	14661444	413	383	A	1.58	6.89E-06
RS28880069:14661518:C:G	8	14661518	413	383	C	0.65	1.62E-05
RS138769756:14664899:C:T	8	14664899	413	383	T	1.53	2.06E-05
RS187891412:14665482:C:A	8	14665482	413	383	A	1.56	1.09E-05
RS1031054:14668259:C:T	8	14668259	413	383	T	1.56	1.14E-05
RS2250879:14668742:G:C	8	14668742	413	383	G	0.63	5.96E-06
RS2250963:14669239:T:A	8	14669239	413	383	T	0.61	1.77E-06
RS2034005:14670877:C:G	8	14670877	413	383	C	0.63	5.67E-06
RS2251199:14671281:A:G	8	14671281	413	383	A	0.62	4.15E-06
RS2483307:84564127:G:A	10	84564127	413	383	G	1.55	2.14E-05
RS4488143:84596866:C:T	10	84596866	413	383	C	1.59	8.42E-06
RS485907:84599583:T:A	10	84599583	413	383	T	1.59	7.57E-06
RS168201:84610081:G:A	10	84610081	413	383	G	1.59	7.48E-06
RS7171524:94738563:G:C	15	94738563	413	383	G	0.59	1.72E-05
RS17629107:94740359:C:T	15	94740359	413	383	C	0.59	1.09E-05
RS6497177:94741598:T:G	15	94741598	413	383	T	0.59	1.10E-05
RS12909327:94742652:G:C	15	94742652	413	383	G	0.64	3.05E-05
RS28813744:94744876:T:C	15	94744876	413	383	T	0.58	1.35E-05
RS28397663:47328183:C:T	17	47328183	466	403	T	0.65	3.23E-05
RS34666276:47379486:T:C	17	47379486	466	403	C	0.65	4.06E-05
RS9889262:47398070:T:A	17	47398070	466	403	A	0.65	4.09E-05
RS12940887:47402807:C:T	17	47402807	466	403	T	0.65	4.09E-05
RS62076439:47404628:G:T	17	47404628	466	403	T	0.65	4.13E-05
RS35587648:47418178:G:A	17	47418178	466	403	A	0.65	3.78E-05
RS35073649:47422510:C:T	17	47422510	466	403	T	0.65	3.92E-05
RS7207729:47423740:C:T	17	47423740	466	403	T	0.65	3.82E-05
RS6504608:47424681:C:A	17	47424681	466	403	A	0.65	3.83E-05
RS57816977:4012466:T:C	18	4012466	413	383	C	0.54	1.18E-05
RS17653931:4019781:A:T	18	4019781	413	383	T	0.54	2.84E-05
RS62083652:4019804:C:T	18	4019804	413	383	T	0.53	1.86E-05
RS2335226:14949034:C:G	19	14949034	413	383	G	0.61	2.75E-05
RS10413393:14950428:C:A	19	14950428	413	383	A	0.62	4.96E-05

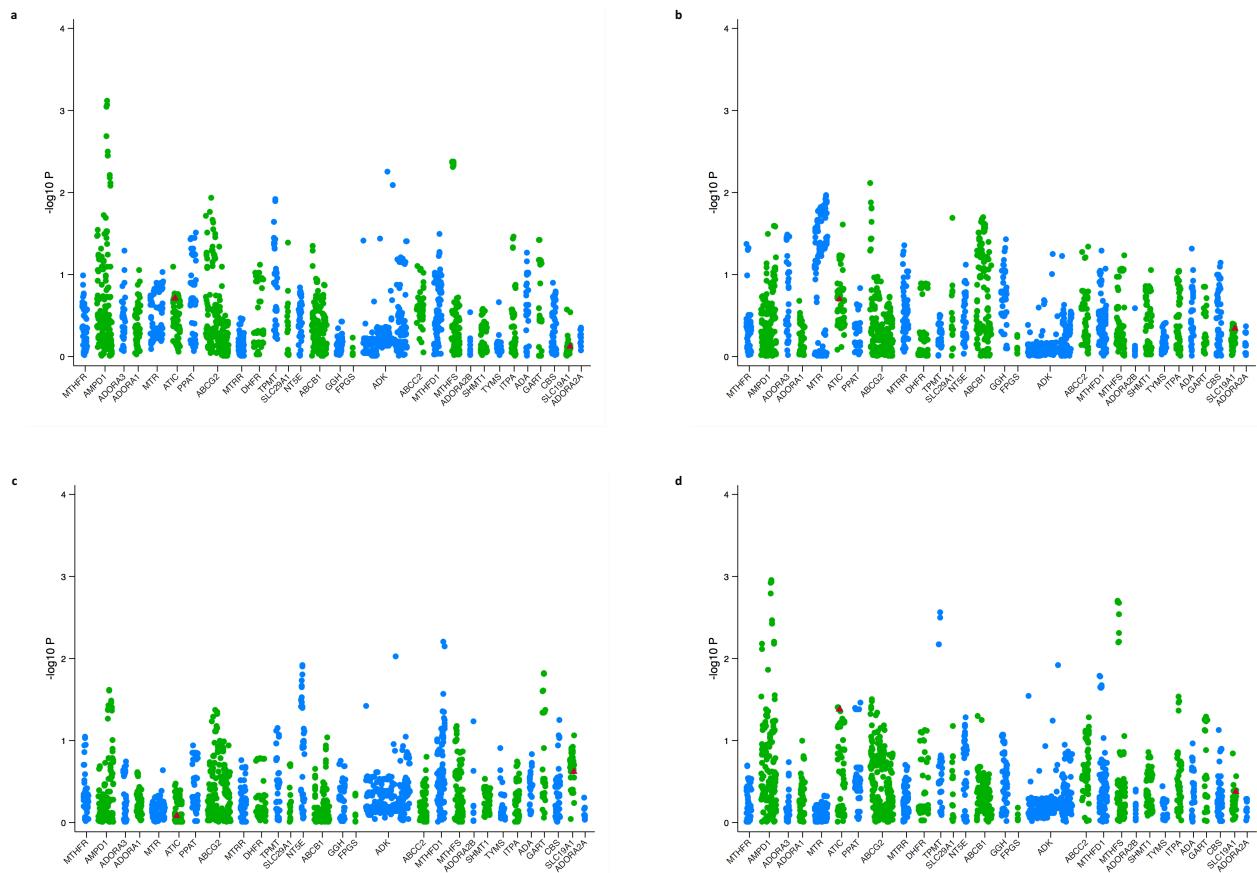
Supplementary Figure 1. Manhattan plots of the genome-wide association analyses for DAS28 (a), CRP (b), SJC28 (c) and TJC28 (d). The dashed line indicates the P-value for 5×10^{-8} .



Supplementary Figure 2. QQ-plots of the genome-wide association analyses for DAS28 (a), CRP (b), SJC28 (c) and TJC28 (d).



Supplementary Figure 3. Results for methotrexate metabolism candidate genes for DAS28 (a), CRP (b), SJC28 (c) and TJC28 (d). Genes are plotted in chromosome-basepair order. SNPs previously associated in more than one study, rs2372536 in *ATIC* and rs1051266 in *SLC19A1*, are indicated by a red triangle.



Appendix I

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CARDERA

CARDERA Genetics Cohort

CARDERA-1 Trial

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CARDERA-2 Trial

Scott IC, Ibrahim F, Simpson G, Kowalczyk A, White-Alao B, Hassell A, Plant M, Richards S,
Walker D, Scott DL.

CARDERA-1 and 2 Genetics Cohort

Scott IC, Lewis CM, Cope AP, Steer S, Spain S.

Appendix II

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