Supplementary Table S1. Anti-TNF-α treatment profile of study cohort.

		RF positive	Anti-CCP positive	HLA-DRB1 0404	CD226 (TC)	CD226 (CC)	CD226 total
Adalimumab	n positive	77	50	25	62	36	98
	n available	100	67	119	119	119	119
	%	77.0%	74.6%	21.0%	52.1%	30.3%	82.4%
Etanercept	n positive	47	34	9	32	25	57
	n available	64	44	70	70	70	70
	%	73.4%	77.3%	12.9%	45.7%	35.7%	81.4%
Infliximab	n positive	19	7	12	21	7	28
	n available	28	12	35	35	35	35
	%	67.9%	58.3%	34.3%	60.0%	20.0%	80.0%
Certoluzimab	n positive	5	3	3	6	2	8
	n available	8	5	8	8	8	8
	%	62.5%	60.0%	37.5%	75.0%	25.0%	100.0%
Golimumab	n positive	1	0	1	4	0	4
	n available	2	1	4	4	4	4
	%	50.0%	0.0%	25.0%	100.0%	0.0%	100.0%
Combined	n positive	149	94	50	125	70	195
	n available	202	129	236	236	236	236
	%	73.8%	72.9%	21.2%	53.0%	29.7%	82.6%

RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide; CD226 (TC): heterozygous SNP carrier; CD226 (CC): homozygous SNP carrier; CD226 total: combined TC and CC carriers.

Supplementary Table S2. Association of factors with baseline DAS28 score.

Factor	Group	Group No.s	Group %	Group mean Baseline DAS28	*p*-value
Gender	Male	47	23.9%	5.16	0.127
	Female	150	76.1%	5.47	
Baseline cDMARD	No	21	10.7%	5.50	0.694
	Yes	176	89.3%	5.39	
KIR2DL2	0	80	40.6%	5.53	0.203
	1	117	59.4%	5.31	
KIR2DS2	0	76	38.6%	5.53	0.233
	1	121	61.4%	5.31	
HLAC1	0	25	12.7%	5.19	0.362
	1	172	87.3%	5.43	
HLAC2	0	86	43.7%	5.58	0.070
	1	111	56.3%	5.26	
HLA03	0	155	78.7%	5.42	0.658
	1	42	21.3%	5.32	
HLA0101	0	138	70.1%	5.38	0.753
	1	59	29.9%	5.44	
HLA0401	0	99	50.3%	5.41	0.907
	1	98	49.7%	5.39	
HLA0404	**0**	**155**	**78.7%**	**5.30**	**0.038**
	1	**42**	**21.3%**	**5.75**	
HLA1001	0	188	95.4%	5.37	0.196
	1	9	4.6%	5.92	
HLADRBTNL	11	139	70.6%	5.39	0.932
	12	52	26.4%	5.41	
	22	6	3.0%	5.58	
PTPRC	11	155	78.7%	5.41	0.353
	12	41	20.8%	5.38	
	22	1	0.5%	3.64	
AFF	11	50	25.4%	5.42	0.981
	12	108	54.8%	5.38	
	22	39	19.8%	5.40	
CD226	11	30	15.2%	5.42	0.921
	12	108	54.8%	5.37	
	22	59	29.9%	5.44	
myD	11	134	68.0%	5.48	0.307
	12	58	29.4%	5.25	
	22	5	2.5%	4.85	
CHUK	11	61	31.0%	5.22	0.403
	12	89	45.2%	5.48	
	22	47	23.9%	5.46	
MTHFR1	11	88	44.7%	5.43	0.928
	12	82	41.6%	5.38	
	22	27	13.7%	5.34	
MTHFR2	11	93	47.2%	5.30	0.567
	12	85	43.1%	5.50	
	22	19	9.6%	5.44	

Allele genotypes: 1, present; 0, absent. SNP genotypes: 11, wildtype; 12, heterozygous carrier; 22 homozygous carrier.

Supplementary Table S3. Association of genetic factors with EULAR response.

Factor	Genotype Group	EULAR RESPONSE, genotype n (%)						p-value
		NON n	%	MODERATE n	%	GOOD n	%	
KIR2DL2	0	23	22.3%	42	40.8%	38	36.9%	0.601
	1	37	27.4%	48	35.6%	50	37.0%	
KIR2DS2	0	22	22.2%	40	40.4%	37	37.4%	0.635
	1	38	27.3%	50	36.0%	51	36.7%	
HLAC1	0	8	27.6%	8	27.6%	13	44.8%	0.463
	1	52	24.9%	82	39.2%	75	35.9%	
HLAC2	0	25	23.4%	44	41.1%	38	35.5%	0.626
	1	35	26.7%	46	35.1%	50	38.2%	
HLA03	0	45	24.2%	68	36.6%	73	39.2%	0.388
	1	15	28.8%	22	42.3%	15	28.8%	
HLA0101	0	41	24.4%	65	38.7%	62	36.9%	0.877
	1	19	27.1%	25	35.7%	26	37.1%	
HLA0401	0	33	26.6%	44	35.5%	47	37.9%	0.728
	1	27	23.7%	46	40.4%	41	36.0%	
HLA0404	0	51	27.3%	74	39.6%	62	33.2%	0.060
	1	9	17.6%	16	31.4%	26	51.0%	
HLA1001	0	57	24.9%	87	38.0%	85	37.1%	0.849
	1	3	33.3%	3	33.3%	3	33.3%	
HLADRBTNL	11	40	23.5%	62	36.5%	68	40.0%	0.488
	12	18	29.5%	24	39.3%	19	31.1%	
	22	2	28.6%	4	57.1%	1	14.3%	
PTPRC	11	41	22.2%	75	40.5%	69	37.3%	0.188
	12	19	37.3%	14	27.5%	18	35.3%	
	22	0	0.0%	1	50.0%	1	50.0%	
AFF	11	41	22.2%	75	40.5%	69	37.3%	0.886
	12	19	37.3%	14	27.5%	18	35.3%	
	22	0	0.0%	1	50.0%	1	50.0%	
CD226	11	7	17.1%	13	31.7%	21	51.2%	0.202
	12	36	28.6%	51	40.5%	39	31.0%	
	22	17	23.9%	26	36.6%	28	39.4%	
myD88	11	44	27.3%	64	39.8%	53	32.9%	0.220
	12	13	18.6%	24	34.3%	33	47.1%	
	22	3	42.9%	2	28.6%	2	28.6%	
CHUK	11	22	27.8%	31	39.2%	26	32.9%	0.834
	12	23	22.1%	40	38.5%	41	39.4%	
	22	15	27.3%	19	34.5%	21	38.2%	
MTHFR1	11	27	25.0%	47	43.5%	34	31.5%	**0.045**
	12	22	22.2%	30	30.3%	47	47.5%	
	22	11	35.5%	13	41.9%	7	22.6%	
MTHFR2	11	32	27.4%	44	37.6%	41	35.0%	0.745
	12	21	21.6%	36	37.1%	40	41.2%	
	22	7	29.2%	10	41.7%	7	29.2%	

Supplementary Table S4. Association of genetic factors with change in DAS28 score over 6 months treatment.

Factor	Group	Group No.s	Group %	Group mean delta DAS28	p value
KIR2DL2	0	103	43.3%	-1.89	0.398
	1	135	56.7%	-1.71	
KIR2DS2	0	99	41.6%	-1.91	0.320
	1	139	58.4%	-1.70	
HLAC1	0	29	12.2%	-1.76	0.929
	1	209	87.8%	-1.79	
HLAC2	0	107	45.0%	-1.84	0.684
	1	131	55.0%	-1.75	
HLA03	0	186	78.2%	-1.86	0.178
	1	52	21.8%	-1.51	
HLA0101	0	168	70.6%	-1.76	0.708
	1	70	29.4%	-1.85	
HLA0401	0	124	52.1%	-1.83	0.653
	1	114	47.9%	-1.74	
HLA0404	0	187	78.6%	-1.67	**0.033**
	1	51	21.4%	-2.22	
HLA1001	0	229	96.2%	-1.80	0.489
	1	9	3.8%	-1.41	
HLADRBTNL	11	170	86.3%	-1.89	0.329
	12	61	31.0%	-1.55	
	22	7	3.6%	-1.42	
PTPRC	11	185	93.9%	-1.85	0.281
	12	51	25.9%	-1.53	
	22	2	1.0%	-3.00	
AFF	11	59	29.9%	-1.61	0.588
	12	126	64.0%	-1.81	
	22	53	26.9%	-1.93	
CD226	11	41	20.8%	-2.35	**0.029**
	12	126	64.0%	-1.57	
	22	71	36.0%	-1.85	
myD88	11	161	81.7%	-1.77	0.916
	12	70	35.5%	-1.84	
	22	7	3.6%	-1.61	
CHUK	11	79	40.1%	-1.65	0.479
	12	104	52.8%	-1.93	
	22	55	27.9%	-1.71	
MTHFR1	11	108	54.8%	-1.71	0.116
	12	99	50.3%	-2.01	
	22	31	15.7%	-1.34	
MTHFR2	11	117	59.4%	-1.67	0.341
	12	97	49.2%	-1.97	
	22	24	12.2%	-1.58	

Supplementary Table S5. The linear model with four potential predictors.

Variable	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	2.48595	0.680512	3.653056	0.000358
Baseline DAS28	-0.66396	0.110541	-6.0065	**1.39E-08**
Concurrent cDMARD	-0.76153	0.386531	-1.97016	0.050674
Baseline HAQ	0.10124	0.157878	0.641258	0.52234
Gender	0.004174	0.301256	0.013856	0.988964

Supplementary Table S6. Sensitivity and specificity of two genetic predictors of anti-TNF-α response.

Biomarker	Prevalence	Responder		Non-responder		Sensitivity TP/(TP+FN)	Specificity TN/(TN+FP)	NPV TN/ (FN+TN)	PPV TP/ (TP+FP)	FDR 1-PPV
		TP	FN	TN	FP					
HLA-DRB1*0404	21%	42	139	52	9	23%	85%	27%	82%	18%
CD226 rs763361	17%	34	146	54	7	19%	89%	27%	83%	17%

TP: true positive; FN: false negative; TN: true negative; FP: false positive; NPV: negative predictive value; PPV, positive predictive value; FDR: false discovery rate.