Both *HLA* class I and II regions identified as genome-wide significant susceptibility loci for adult-onset Still's disease in Chinese individuals

SUPPLEMENTARY INFORMATION

Li Z, *et al. Ann Rheum Dis* 2019; 79:1–2. doi: 10.1136/annrheumdis-2019-215239

Table S1. Primers for Sanger sequencing confirmation

Variant	Type	Primer (5' to 3')	Melting Temperature	Product size (bp)
rs9268791	Forward	TGGGTAACGAGGAGCTGAAT	57.2	484
	Reverse	AGGGCACCAAGTCCAAAGA	57.9	
	Sequencing	CTGCCAGGTTCATGCCATTC		
rs3094178	Forward	AGATGGGAGCAGCCAGAAG	57.3	686
	Reverse	GGAGCCAATCCTCACAAGC	57.9	
	Sequencing	TTGAGGAAGAACAAATACTA		
rs514410	Forward	TTGACCGACTGGCTGAATG	57.2	962
	Reverse	GCTGAGGTGGGAGGATTGC	59.9	
	Sequencing	AAGGTGGTAGGGAATAGGTT		

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Table S2. Association analysis for rs514410 (*VEGFC*)

Analysis[a]	RAF in cases[b]	RAF in controls[b]	OR	SE	P values	P_het
Discovery	0.097	0.046	2.252	0.173	2.68E-06	
Replication	0.088	0.049	1.774	0.602	3.41E-01	
Fixed effect meta-analysis	-	-	2.211	0.166	1.81E-06	0.703
Cochran-Mantel-Haenszel analysis	-	-	2.192	0.164	9.68E-07	-

RAF, frequency of risk allele; OR, odds ratio; SE, stand error; P_het, p value for heterogeneity test across different cohorts using Cochran's Q test. [a]The discovery data set is comprised of 247 cases and 2,163 controls from the Northern and Central China; The replication data set is comprised of 17 cases and 257 controls from the Southern China. The fixed effect meta-analysis and Cochran-Mantel-Haenszel analysis are the combined analyses. [b]Risk allele is A allele.

Table S3. Regulatory and epigenomic annotation of the SNPs with maximum evidence for being located in regulatory regions

SNP	Association p value	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	RegulomeDB score[a]
rs3115628	2.92E-08	ESC, LNG, IPSC, FAT, STRM, BRST, BLD, MUS, BRN, SKIN, LIV, GI, HRT, SPLN, BONE	ESC, ESDR, LNG, IPSC, FAT, BRST, BLD, STRM, BRN, SKIN, VAS, LIV, GI, ADRL, PANC, MUS, THYM, HRT, SPLN, BONE	IPSC,BLD,BLD,BLD,SKIN,BLD	JUND	Nrf1, TATA	1f
rs2073044	2.62E-08	SKIN, CRVX, VAS	ESC, ESDR, FAT, STRM, MUS, SKIN, KID, GI, LNG, CRVX, BRST, VAS, BRN, BONE		CFOS	HDAC2, NF-E2, NF-Y, Pax-5	1f
rs9268528	4.44E-13	SKIN, BRN	IPSC, ESC, BRST, BLD, SKIN, GI, THYM, HRT, BRN	BLD,BLD		AP-1, BDP1, CACD, CHD2, GR, MAZ, PPAR, SP1, STAT, Sp4, ZNF263	1f
rs9268544	3.85E-13					ATF3, BHLHE40, Myc, NF-E2, SREBP, TFE	1f
rs3135365	1.83E-08	ESDR	ESDR			Dobox4, Mef2, Pou3f1	1f

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SNP	Association p value	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	RegulomeDB score[a]
rs2395171	3.09E-07		FAT, LIV, GI				1f
rs14004	1.36E-12	ESC, IPSC, FAT, STRM, BRST, BLD, LIV, BRN, GI, ADRL, KID, LNG, MUS, PLCNT, THYM, HRT, PANC, SPLN, CRVX, SKIN, BONE	ESC, IPSC, FAT, BLD, LIV, BRN, GI, ADRL, MUS, THYM, SPLN	ESC,ESDR,ESDR,ESC,BLD,BLD,BLD,BLD,BLD,BLD,SKIN,ADRL,MUS,MUS,THYM,GI,OVRY,GI,BLD,BLD	NFKB,POL2,BCL3,BCLAF1,CFOS,OCT2,PAX5C20,POL24H8,POU2F2,RAD21,RFX5,SIN3AK20,TAF1,TBP,WHIP,YY1,SP1,USF2		1f
rs9268657	8.80E-13	BLD, FAT, LIV, BRN, GI, ADRL, MUS, THYM, HRT, SPLN	BLD, FAT, BRN, GI, THYM, LNG, MUS, SPLN				1f
rs9268831	8.85E-15	ESC, LNG, FAT, STRM, BRST, BLD, BRN, SKIN, GI, ADRL, KID, MUS, THYM, HRT, PANC, PLCNT, SPLN	ESDR, BRST, BLD, SKIN, FAT, GI, MUS, PLCNT, PANC, SPLN	LNG,MUS,GI,BLD,SKIN	POL2,CMYC,HAE2F1	Hsf	1f
rs9268832	3.41E-18	ESC, LNG, FAT, STRM, BRST, BLD, BRN, SKIN, GI, ADRL, KID, MUS, THYM,	ESDR, BRST, BLD, SKIN, FAT, GI, MUS, PLCNT, PANC, SPLN	LNG,BLD	POL2,CMYC,HAE2F1		1f

SNP	Association p value	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	RegulomeDB score[a]
		HRT, PANC, PLCNT, SPLN					
rs9268833	1.77E-13	ESC, LNG, FAT, BRST, BLD, STRM, SKIN, BRN, GI, ADRL, KID, MUS, THYM, HRT, PANC, PLCNT, SPLN	ESDR, BRST, BLD, SKIN, FAT, GI, MUS, PLCNT, PANC, SPLN				1f
rs9268835	1.72E-13	ESC, FAT, BRST, BLD, STRM, SKIN, BRN, GI, ADRL, KID, MUS, THYM, HRT, PANC, PLCNT, SPLN, LNG	ESDR, BRST, BLD, SKIN, FAT, GI, MUS, PLCNT, PANC, SPLN			ERalpha-a, Esr2, RXRA	1f
rs6903608	9.67E-11	FAT, BRST, BLD, SKIN, BRN, GI, ADRL, MUS, THYM, PANC, PLCNT, HRT, SPLN, LNG	ESDR, BRST, BLD, SKIN, FAT, GI, SPLN			CTCF, EBF, SMC3, Smad	1f

SNP	Association p value	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	RegulomeDB score[a]
rs9268864	5.08E-15	BRN, PLCNT, BLD	ESDR, ESC, IPSC, BLD			Cdx, DMRT2, DMRT3, Hbp1, Isl2, Lhx3, Pou1f1, Pou3f2, Pou3f4, Pou4f3, Sox, Zfp187	2b
rs9268880	2.16E-10	PLCNT, BLD				Foxa, Foxj1, Foxk1, Foxo, GR, HDAC2, Nanog, Sox, p300	1f
rs9405040	NA	BLD, FAT, BRN, GI	BLD	BLD			1f
rs9269070	NA	ESC, BLD, FAT, BRN, HRT, GI	BLD, FAT, GI, SPLN	BLD		CDP,Fox,Foxa,Foxf2,Foxj1,Pou3f3	1f
rs9269078	7.05E-09	ESC, BLD, FAT, BRN, HRT, GI	IPSC, BLD, FAT, BRN, GI, SPLN	BLD,BLD,BLD,BLD,BLD		Maf, Myf, Pax-4	1c
rs9269079	6.77E-09	ESC, BLD, FAT, BRN, HRT, GI	IPSC, BLD, FAT, BRN, GI, THYM, SPLN	BLD,BLD,BLD,BLD,BLD		CEBPA, CEBPB, EWSR1-FLI1, Pou2f2, STAT, p300	2b

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SNP	Association p value	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	RegulomeDB score[a]
rs9269080	9.88E-09	ESC, BLD, FAT, BRN, HRT, GI	IPSC, BLD, FAT, BRN, GI, THYM, SPLN	BLD,BLD,BLD,BLD,BLD		E2F, Evi-1, HDAC2	1b
rs9269081	3.62E-10	ESC, BLD, FAT, BRN, HRT, GI	ESDR, ESC, IPSC, BLD, FAT, BRN, GI, THYM, SPLN	BLD,BLD,BLD,BLD,BLD		CIZ, DMRT7, Mef2	1d
rs9269084	1.55E-08	ESC, BLD, FAT, BRN, GI, HRT	ESC, ESDR, IPSC, BLD, FAT, BRN, GI, THYM, LNG, HRT, SPLN	ESC,BLD,BLD,BLD,BLD	ELF1,OCT2,POL2,POL24H8,POU2F2,TBP	Ets, Gm397	2b
rs12215313	1.22E-15	ESC, BLD, FAT, BRN, GI, HRT	ESC, ESDR, IPSC, BLD, FAT, BRN, GI, THYM, LNG, HRT, SPLN	ESC,ESDR,ESC,IPSC,BLD,BLD,BLD,BLD,BLD,BLD,SKIN,GI,THYM,PANC,GI,BLD,BLD,BLD	EGR1,ELF1,OCT2,POL2,POL24H8,POU2F2,TAF1,TBP,PU1	EBF, Hsf	2b
rs7755212	NA	ESC, BLD, FAT, BRN, HRT, GI	ESDR, ESC, IPSC, BLD, FAT, BRN, GI, THYM, HRT, SPLN	ESC,ESDR,ESDR,ESC,IPSC,IPSC,BLD,BLD,BLD,BLD,BLD,BLD,BLD,BLD,SKIN,HRT,GI,KID,MUS,THYM,PANC,GI,BLD,MUS,BLD,BLD,SKIN	EGR1,ELF1,POL2,POL24H8,RFX5,TAF1,PU1,CFOS	AP-1,FXR,PU.1,STAT,VDR	1b

SNP	Association p value	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	RegulomeDB score[a]
rs7773182	NA	ESC, BLD, FAT, BRN, HRT, GI	ESDR, ESC, IPSC, BLD, FAT, BRN, GI, THYM, HRT, SPLN	ESC,ESDR,ESDR,ESC,IPSC,IPSC,BLD,BLD,BLD,BLD,BLD,BLD,BLD,BLD,GI,KID,MUS,THYM,GI,BLD,MUS,BLD,BLD,SKIN	EGR1,ELF1,POL2,POL24H8,RFX5,TAF1,PU1,CFOS	CEBPA,CEBPB	2a
rs7739203	NA	ESC, BLD, FAT, BRN, HRT, GI	ESDR, ESC, IPSC, BLD, FAT, BRN, GI, THYM, HRT, SPLN	ESC,IPSC,BLD,BLD,BLD,BLD,BLD,BLD,MUS,THYM,GI,BLD,BLD	RFX5,TBP,CFOS	Hoxa5,Ncx,Nkx2,TCF4,Zfp187	1f
rs28895247	7.37E-17	GI	BLD		CTCF	GR, HNF4, PPAR, Sin3Ak-20	2b
rs9405112	9.71E-16	BRN, HRT, GI	GI		CTCF	Pou2f2	1f
rs9378212	3.71E-17	BRN, HRT	GI	ESDR	CTCF	HDAC2, Mef2, SRF, Sox, TATA	1b
rs5020946	6.83E-14	BLD	BLD, LNG	BLD		AP-2, STAT	1f

SNP	Association p value	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	RegulomeDB score[a]
rs12191360	4.61E-09	BLD	BLD, SPLN			Hoxa10, Hoxa9, Hoxb13, Hoxb9, Hoxd10, Pou6f1, Zfp105	1f
rs28366212	4.21E-14	ESDR, ESC, FAT, BLD, LIV, BRN, GI, KID, THYM, HRT, LNG, MUS, SPLN	ESC, ESDR, IPSC, FAT, BLD, GI, THYM	BLD,BLD,BLD,BLD,BLD	POL24H8	Foxa, Maf, PU.1, SRF, STAT, TFIIA, p300	2b
rs28366213	4.21E-14	ESDR, ESC, FAT, BLD, LIV, BRN, GI, KID, THYM, HRT, LNG, MUS, SPLN	ESC, ESDR, IPSC, FAT, BLD, GI, THYM	BLD,BLD,BLD,BLD,BLD	POL24H8	SRF, TATA, TFIIA, YY1	2b
rs28366298	1.83E-15	ESDR	ESDR, BLD				1f
rs9270911	2.21E-09	FAT, BLD, BRN, GI, MUS, HRT	FAT, BLD, LIV, BRN, GI	BLD,BLD,BLD,BLD,BLD,BLD,BLD,BLD	NFKB,POL2,TAF1	Pou5f1	1f
rs586610	2.70E-07	FAT, BLD, BRN, GI, MUS, HRT	FAT, BLD, LIV, BRN, GI	BLD,BLD,BLD,BLD,BLD,BLD,BLD,BLD	NFKB,TBP,POL2,TAF1	EWSR1-FLI1	1f

SNP	Association p value	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	RegulomeDB score[a]
rs9270923	2.11E-10	BLD, FAT, BRN, GI, HRT	FAT, BLD, LIV, BRN, GI, PANC	BRST,BLD,BLD, BLD,BLD,BLD,B LD,BLD,MUS,M US,BLD,MUS,BL D	NFKB,POL2,R FX5,TBP	CIZ, ELF1, Ik-2, NF-AT, STAT	2b
rs9270924	3.24E-09	BLD, FAT, BRN, GI, HRT	FAT, BLD, LIV, BRN, GI, PANC	BRST,BLD,BLD, BLD,BLD,BLD,B LD,BLD,MUS,M US,BLD,MUS,BL D	NFKB,POL2,R FX5,TBP	CDP, ELF1, Ik-2, Mef2, NF-AT, NF-Y, RFX5, STAT	2b
rs9270925	3.24E-09	BLD, FAT, BRN, GI, HRT	FAT, BLD, LIV, BRN, GI, PANC	BRST,BLD,BLD, BLD,BLD,BLD,B LD,BLD,SKIN,M US,MUS,BLD,M US,BLD	POL2,RFX5,SR F,TBP,NFKB	Irf, Osf2	2b
rs9270926	3.24E-09	BLD, FAT, BRN, GI, HRT	FAT, BLD, LIV, BRN, GI, PANC	BRST,BLD,BLD, BLD,BLD,BLD,B LD,BLD,SKIN,M US,MUS,BLD,M US,BLD	POL2,RFX5,SR F,TBP,NFKB	Foxp3, GATA, Irf, Osf2	2b
rs9271055	7.67E-10	GI, BLD	BLD, FAT, HRT	BLD,BLD,BLD,B LD,BLD	BATF,EGR1,N FKB	COMP1, Ets, Nanog, p300	1d
rs9271100	1.15E-08	BLD, GI	ESC, IPSC, BLD, FAT, BRN, PLCNT, GI	BLD	CTCF		1f

SNP	Association p value	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	RegulomeDB score[a]
rs9271155	3.52E-11	ESC, ESDR, IPSC, FAT, STRM, BRST, BLD, SKIN, BRN, GI, KID, HRT, MUS, BONE	ESC, ESDR, IPSC, FAT, BRST, BLD, SKIN, BRN, GI, ADRL, KID, PANC, THYM, PLCNT, MUS, CRVX, BONE	ESDR,ESDR,ESC,BRST,BLD,BLD,BLD,BLD,BLD,BLD,BLD,BLD,SKIN,GI,KID,THYM,BLD,CRVX,BRST,MUS,BLD,SKIN	NFKB,EBF1,OCT2,POL2,POU2F2,TAF1,POL24H8,RFX5,STAT1,GATA1	AP-2, BCL, Evi-1, Gcm1, INSM1, Pbx3, YY1	2b
rs9271156	9.25E-09	ESC, ESDR, IPSC, FAT, STRM, BRST, BLD, SKIN, BRN, GI, KID, HRT, MUS, BONE	ESC, ESDR, IPSC, FAT, BRST, BLD, SKIN, BRN, GI, ADRL, KID, PANC, THYM, PLCNT, MUS, CRVX, BONE	ESDR,ESDR,ESC,BRST,BLD,BLD,BLD,BLD,BLD,BLD,BLD,BLD,SKIN,GI,KID,THYM,BLD,CRVX,BRST,MUS,BLD,SKIN	NFKB,EBF1,OCT2,POL2,POU2F2,SP1,TAF1,POL24H8,RFX5,STAT1,GATA1	AP-2, BCL, Gcm1, INSM1, Pbx3, YY1	2b
rs9271159	4.32E-10	ESC, ESDR, IPSC, FAT, STRM, BRST, BLD, SKIN, BRN, GI, KID, HRT, MUS, BONE	ESC, ESDR, IPSC, FAT, BRST, BLD, SKIN, BRN, GI, ADRL, KID, PANC, THYM, PLCNT, MUS, CRVX, BONE	ESC,ESDR,ESDR,ESDR,ESDR,ESC,IPSC,BRST,BLD,BLD,BLD,BLD,BLD,BLD,BLD,SKIN,SKIN,SKIN,SKIN,BRN,GI,KID,LNG,MUS,MUS,PLCNT,THYM,OVRY,PANC,MUS,GI,BLD,CRVX,BRST,MUS,MUS,VAS,BLD,BLD,BRN,SKIN,LNG	NFKB,CHD2,EBF1,OCT2,POL2,POU2F2,RFX5,SP1,TAF1,TBP,POL24H8,STAT1,USF2,GTF2F1,GATA1,KAP1	RFX5, STAT	2b

SNP	Association p value	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	RegulomeDB score[a]
rs9271160	4.10E-10	ESC, ESDR, IPSC, FAT, STRM, BRST, BLD, SKIN, BRN, GI, KID, HRT, MUS, BONE	ESC, ESDR, IPSC, FAT, BRST, BLD, SKIN, BRN, GI, ADRL, KID, PANC, THYM, PLCNT, MUS, CRVX, BONE	ESC,ESDR,ESDR,ESDR,ESDR,ESC,IPSC,BRST,BLD,BLD,BLD,BLD,BLD,BLD,BLD,SKIN,SKIN,SKIN,SKIN,BRN,GI,KID,LNG,MUS,MUS,PLCNT,THYM,OVRY,PANC,MUS,GI,BLD,CRVX,BRST,MUS,MUS,VAS,BLD,BLD,BRN,SKIN,LNG	NFKB,CHD2,EBF1,OCT2,POL2,POU2F2,RFX5,SP1,TAF1,TBP,POL24H8,STAT1,USF2,GTF2F1,GATA1,KAP1	RFX5, STAT	2b
rs9271161	4.10E-10	ESC, ESDR, IPSC, FAT, STRM, BRST, BLD, SKIN, BRN, GI, KID, HRT, MUS, BONE	ESC, ESDR, IPSC, FAT, BRST, BLD, SKIN, BRN, GI, ADRL, KID, PANC, THYM, PLCNT, MUS, CRVX, BONE	ESC,ESDR,ESDR,ESDR,ESDR,ESC,LNG,IPSC,IPSC,BRST,BLD,BLD,BLD,BLD,BLD,BLD,SKIN,SKIN,SKIN,SKIN,ADRL,BRN,BRN,HRT,GI,GI,KID,LNG,MUS,MUS,PLCNT,GI,THYM,GI,OVRY,PANC,MUS,GI,LNG,BLD,CRVX,BRST,MUS,MUS,VAS,BLD,BLD,BRN,S	NFKB,CHD2,EBF1,POL2,RFX5,SP1,TAF1,TBP,YY1,CFOS,CJUN,STAT1,USF2,FOSL1,GTF2F1,NFYA,NFYB,GATA1,KAP1	STAT	2a

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SNP	Association p value	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	RegulomeDB score[a]
				KIN,SKIN,LNG			
rs9271168	6.39E-09	ESC, ESDR, IPSC, FAT, STRM, BRST, BLD, SKIN, BRN, GI, KID, HRT, MUS, LNG, BONE	ESC, ESDR, IPSC, FAT, BRST, BLD, SKIN, BRN, GI, ADRL, KID, PANC, THYM, PLCNT, MUS, CRVX, BONE	ESC,ESDR,ESDR,ESDR,ESDR,ESC,LNG,IPSC,IPSC,BRST,BLD,BLD,BLD,BLD,BLD,BLD,SKIN,SKIN,SKIN,SKIN,ADRL,BRN,GI,GI,KID,LNG,MUS,MUS,PLCNT,GI,THYM,GI,OVRY,PANC,MUS,GI,LNG,BLD,CRVX,BRST,MUS,MUS,VAS,BLD,BLD,BRN,SKIN,SKIN,LNG	BATF,CHD2,NFKB,RFX5,YY1,CFOS,CJUN,STAT1,USF2,FOSL1,GTF2F1,JUNB,JUND,NFYA,TAL1,STAT3,GATA1,POL2,KAP1	AP-1, AP-2, BATF, Bach1, Bach2, GATA, GR, HMGN3, Irf, KAP1, Maf, Myc, Nkx2, Nkx3, Nrf-2, PRDM1, RXRA, STAT, TCF4, p300	2a
rs9271170	6.39E-09	ESC, ESDR, IPSC, FAT, STRM, BRST, BLD, SKIN, BRN, GI, KID, HRT, MUS, LNG, BONE	ESC, ESDR, IPSC, FAT, BRST, BLD, SKIN, BRN, GI, ADRL, KID, PANC, THYM, PLCNT, MUS, CRVX, BONE	ESC,ESDR,ESDR,ESDR,ESDR,ESC,LNG,IPSC,IPSC,BRST,BLD,BLD,BLD,BLD,BLD,BLD,SKIN,SKIN,SKIN,SKIN,GI,GI,MUS,GI,GI,PANC,GI,BLD,	BATF,CHD2,NFKB,RFX5,YY1,CFOS,CJUN,STAT1,FOSL1,JUNB,TAL1,STAT3,GATA1,POL2,KAP1	Bcl6b, NRSF, STAT, Sp100	1f

SNP	Association p value	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	RegulomeDB score[a]
				CRVX,BRST,MUS,MUS,BLD,BLD,BRN,SKIN,SKIN,LNG			
rs9271171	NA	ESC, ESDR, IPSC, FAT, STRM, BRST, BLD, SKIN, BRN, GI, KID, HRT, MUS, LNG, BONE	ESC, ESDR, IPSC, FAT, BRST, BLD, SKIN, BRN, GI, ADRL, KID, PANC, THYM, PLCNT, MUS, CRVX, BONE	ESC,ESDR,ESDR,ESDR,ESDR,ESC,IPSC,IPSC,BRST,BLD,BLD,BLD,BLD,BLD,BLD,BLD,SKIN,SKIN,GI,GI,MUS,GI,GI,BLD,CRVX,BRST,MUS,MUS,BLD,BLD,BRN,SKIN,SKIN,LNG	BATF,CHD2,EBF1,RFX5,YY1,POL2,NFKB,CFOS,CJUN,FOSL1,JUNB,TAL1,STAT3,GATA1,KAP1	Dobox4,Lmo2-complex,SIX5	2b
rs9271199	1.61E-08	ESC, ESDR, IPSC, BLD, BRN, GI	ESC, IPSC, BRST, BLD, SKIN, GI, KID, PANC, THYM	BLD,BLD	BATF,MEF2A, MEF2C	HNF1, Ncx	2b
rs7451962	3.25E-07	ESDR	ESC, ESDR, IPSC, BLD, THYM, PANC, HRT	ESDR			1f
rs9271331	3.25E-07	ESDR, GI	ESC, ESDR, IPSC, BLD, THYM, PANC	ESDR,IPSC		BDP1,Irf,Klf4,Klf7,SP1,Sp4,TATA, UF1H3BETA	2b

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SNP	Association p value	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	RegulomeDB score[a]
rs9271488	2.76E-13	BLD	BLD				1f
rs200688486	NA	BLD	BLD			STAT	1f
rs9271511	4.37E-13	BLD	BLD, SKIN, GI, THYM, SPLN		POL2,POL24H8 ,TBP	Arid3a, Dbx1, Foxj1, HNF1, Hoxa10, Hoxd10, Hoxd8, Nanog, Ncx, Nkx6-1, Pou2f2, Pou3f2, Pou3f3, TATA, Zfp187	2c
rs9271540	3.43E-13	BLD, GI, BRN	ESC, IPSC, BRST, BLD, SKIN, FAT, GI, THYM, SPLN	BLD,BLD,BLD		Arid5a, Cdx2, Foxj2, Rhox11	2b
rs9271549	4.37E-13	BLD, GI, BRN	ESC, IPSC, BRST, BLD, SKIN, FAT, GI, THYM, SPLN	BLD,BLD,BLD,B LD,BLD,BLD	POL2,CTCF,ZN F263	AP-1, CHX10, DBP, Gfi1, PLZF	2b
rs9271567	9.59E-10	BLD, GI, BRN	ESC, IPSC, BRST, BLD, SKIN, FAT, GI, THYM, SPLN	ESC,ESDR,ESDR ,ESDR,ESDR,ES C,IPSC,IPSC,BRS T,BLD,BLD,BLD, BLD,BLD,BLD,B	CTCF,ELF1,OC T2,PAX5C20,P AX5N19,POL2, POL24H8,POU 2F2,RAD21,RF		1f

SNP	Association p value	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	RegulomeDB score[a]
				LD,SKIN,SKIN,BRN,KID,MUS,GI,THYM,MUS,GI,BLD,MUS,BLD,SKIN,SKIN	X5,SIX5,SMC3,TBP,YY1,NFKB,TAF1,NANOG,ZNF263		
rs9271568	1.36E-13	BLD, GI, BRN	ESC, IPSC, BRST, BLD, SKIN, FAT, GI, THYM, SPLN	ESC,ESDR,ESDR,ESDR,ESDR,ESC,IPSC,IPSC,BRST,BLD,BLD,BLD,BLD,BLD,BLD,BLD,SKIN,SKIN,BRN,KID,MUS,THYM,MUS,GI,BLD,BLD,SKIN,SKIN	CTCF,ELF1,OCT2,PAX5C20,PAX5N19,POL2,POL24H8,POU2F2,RAD21,RFX5,SIX5,SMC3,TBP,YY1,NFKB,TAF1,NANOG,ZNF263	Nkx2, Zfp691	1f
rs9271574	4.52E-13	BLD, GI, BRN	ESC, IPSC, BRST, BLD, SKIN, FAT, GI, THYM, SPLN	BLD,BLD,BLD,BLD,BLD,THYM,BLD,BLD	OCT2,PAX5C20,PAX5N19,POL24H8,POU2F2,PU1,SIX5,TBP,POL2,TAF1,NFKB,ZNF263		1f
rs9271583	8.21E-12	BLD, GI, BRN, SKIN	ESC, IPSC, BRST, BLD, SKIN, FAT, GI, THYM, SPLN	BRST,BLD,BLD,BLD,BLD,BLD,BLD,BLD,GI,BLD,BLD	POL2	Cphx, DMRT7, Dobox4, Irf, SIX5	2b
rs2097431	9.40E-08	BLD, GI, BRN, SKIN	ESC, IPSC, BRST, BLD, SKIN, FAT, GI, THYM, SPLN	BRST,BLD,BLD,BLD,BLD,BLD,BLD,BLD,SKIN,THYM,GI,BLD,BLD	MEF2C,NFKB,POL2		1f

SNP	Association p value	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	RegulomeDB score[a]
rs9271586	1.75E-14	BLD, GI, BRN, SKIN	ESC, IPSC, BRST, BLD, SKIN, FAT, GI, THYM, SPLN	BRST,BLD,BLD, BLD,BLD,BLD,B LD,BLD,SKIN,S KIN,GI,THYM,M US,GI,BLD,BRST ,MUS,BLD	BCL11A,MEF2 A,MEF2C,NFK B,SP1,TBP,OC T2,POL2,POU2 F2		1f
rs9271588	1.57E-14	BLD, GI, BRN, SKIN	ESC, IPSC, BRST, BLD, SKIN, FAT, GI, THYM, SPLN	ESDR,BRST,BLD ,BLD,BLD,BLD, BLD,BLD,BLD,S KIN,SKIN,SKIN, MUS,THYM,MU S,GI,BLD,BRST, MUS,BLD,SKIN	BCL11A,MEF2 A,MEF2C,NFK B,OCT2,POU2F 2,RFX5,SP1,TB P	Cdx2, Pdx1	1b
rs9271589	4.56E-13	BLD, GI	ESC, IPSC, BRST, BLD, SKIN, FAT, GI, THYM, SPLN	BRST,BLD,BLD, BLD,BLD,BLD,B LD,BLD,GI,BLD, BLD	NFKB,RFX5,T BP	CACD, FXR, SF1, Zec	1b
rs9271590	1.78E-14	BLD, GI	ESC, IPSC, BRST, BLD, SKIN, FAT, GI, THYM, SPLN	BLD,BLD,BLD,B LD,BLD,BLD,BL D,GI,BLD,BLD	NFKB,RFX5,T BP	CACD, CTCFL, INSM1, Myc, NF-kappaB	2b
rs9271591	1.84E-14	BLD, GI	ESC, IPSC, BRST, BLD, SKIN, FAT, GI, THYM, SPLN	BLD,BLD,BLD,B LD,BLD,BLD,BL D,GI,BLD,BLD	NFKB,RFX5,T BP	CACD, CTCFL, INSM1, NF-kappaB, Pou2f2, Rad21	1b
rs3129765	1.30E-10	BLD, GI	ESC, IPSC, BRST, BLD, SKIN, FAT, GI, THYM, SPLN	BLD,BLD	TBP	TATA	2c

SNP	Association p value	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	RegulomeDB score[a]
rs9271605	3.02E-13	BLD, GI	ESC, IPSC, BRST, BLD, SKIN, FAT, GI, THYM, SPLN	BLD,BLD,BLD	RFX5,TBP	CEBPA, CEBPB, CEBPD, Smad, Zfp105	1d
rs9271687	2.18E-11	BLD	BLD, THYM, GI	BLD,BLD,BLD,BLD	EBF1		2c
rs9271775	5.00E-12	BLD	BLD, THYM				1f
rs3129768	1.47E-10	BLD	FAT, BLD	BLD	EBF1,POL2		1f
rs3104369	4.23E-09	BLD, MUS, GI	ESC, BLD, SPLN, BRST	BLD,BLD,BLD		Pou2f2	1f
rs9272346	8.25E-08	ESC, BLD, GI, MUS, SPLN	ESC, ESDR, IPSC, BRST, BLD, VAS, LNG	BLD,BLD		ERalpha-a,Esr2,Foxj2,HNF4,Klf7, LF-A1,RXRA	1b
rs9272410	5.22E-11	BLD, GI, HRT, MUS, SPLN	ESC, ESDR, IPSC, BLD, VAS, GI, LNG, SPLN	ESC,BLD,BLD,BLD,BLD,BLD,BLD,BLD	NFKB,POL24H8,RFX5	Hoxa9, Hoxb9, Hoxc9, Pdx1	2b

SNP	Association p value	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	RegulomeDB score[a]
rs9272416	8.75E-08	BLD, GI, HRT, LNG, MUS, THYM, SPLN	ESC, ESDR, IPSC, BLD, VAS, GI, LNG, SPLN	ESC,BRST,BLD, BLD,BLD,BLD,B LD,BLD,BLD,TH YM,PANC,BLD, BLD	NFKB,POL24H 8,RFX5,TBP	ERalpha-a,Hic1,R XRA,SP1	2a
rs9272420	1.90E-13	BLD, FAT, BRN, GI, HRT, LNG, MUS, THYM, SPLN	ESC, ESDR, IPSC, BLD, VAS, GI, LNG, MUS, SPLN	ESC,BRST,BLD, BLD,BLD,BLD,B LD,BLD,BLD,GI, THYM,OVRY,PA NC,MUS,BLD,C RVX,BLD	NFKB,ELF1,PO L2,POL24H8,R FX5,TBP	Dobox4, HMG-IY, Myc, NF-kappaB	2b
rs9272491	1.01E-07	BLD, FAT, LIV, BRN, GI, THYM, HRT, LNG, SPLN	BLD, GI, LNG, MUS			Dobox4,Hltf,Mef 2,Pou2f2,SIX5	2b
rs9272492	NA	BLD, FAT, LIV, BRN, GI, THYM, HRT, LNG, SPLN	BLD, GI, LNG, MUS			Mef2,Pou2f2	2b
rs9272494	1.13E-07	BLD, FAT, LIV, BRN, GI, THYM, HRT, LNG, SPLN	BLD, GI, LNG, MUS			CEBPB,Gfi1,Lhx 3,Pax-4,Pou3f2,T EF	2b
rs41269945	1.03E-08	BLD, FAT, LIV, BRN, GI, THYM, HRT	BLD, GI, LNG, HRT, SPLN			HMG-IY, Lhx3	2b

SNP	Association p value	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	RegulomeDB score[a]
rs9272614	3.64E-09	BLD, FAT, LIV, BRN, GI, THYM, HRT	BLD, GI, LNG, HRT, SPLN			AP-1, HMG-IY, Irf, STAT	2b
rs17426593	1.17E-07	BLD, FAT, LIV, BRN, GI, THYM	BLD, LNG, HRT, SPLN	BLD,BLD	POL2,POL24H8	AP-1,Lhx4,NF-Y, RFX5	1f
rs9272723	NA	BLD, FAT, GI	BLD, GI, HRT, LNG, SPLN			Barx1,Cdx2,EBF	1f
rs9273363	4.51E-11	ESDR, ESC, BLD	ESC, ESDR, IPSC, BLD, LNG, PANC, SPLN	BLD,BLD	POL24H8	ATF2, E4BP4, Hsf, LXR	1d
rs1063355	1.19E-06	BLD	ESC, ESDR, BRST, BLD	BLD,BLD,BLD,BLD	EBF1,ELF1,TBP,TCF12	AIRE,HNF1,Nanog	1d
rs1770	3.21E-15	BLD	ESC, ESDR, BRST, BLD, THYM, HRT, SPLN	BLD,GI,BLD	EBF1,ELF1,POL2,TBP,TCF12	Ets, NRSF, Nrf-2	1f
rs1063349	2.57E-06	BLD	ESC, ESDR, BRST, BLD, THYM, HRT, SPLN	BLD,BLD,BLD,BLD	ELF1,POL2,POL24H8	HNF4,TCF4	2b

SNP	Association p value	Promoter histone marks	Enhancer histone marks	DNAse	Proteins bound	Motifs changed	RegulomeDB score[a]
rs2647025	4.30E-13	ESC, BRST, BLD, BRN, GI, THYM, LNG	ESC, IPSC, BRST, BLD, FAT, GI, THYM, HRT, LNG, PANC, MUS, SPLN, CRVX, SKIN	BLD,BLD,BLD	POL2		1f
rs3828796	3.37E-08	ESC, BRST, BLD, BRN, GI, THYM, LNG	ESC, IPSC, BRST, BLD, FAT, GI, THYM, HRT, LNG, PANC, MUS, SPLN, CRVX, SKIN	BLD,BLD,BLD,BLD	POL2,POL24H8	AP-1, ERalpha-a, Esr2, FXR, LXR, RXRA	1f
rs17205563	NA	BLD, GI	IPSC, BRST, BLD, FAT, GI, THYM, HRT, LNG, MUS, SPLN	BLD	POL2,POL24H8	ATF3,Myc,SIRT6,SREBP,ZEB1	2b
rs73410789	1.76E-08	BRN	ESC, IPSC, FAT, STRM, BRST, BLD, SKIN, BRN, THYM, GI, MUS	SKIN	CTCF,SMC3	RFX5	2b
rs762808	2.79E-08	SKIN	IPSC, BLD		ZNF263	CACD, CCNT2, Klf4, Klf7, MAZR, MZF1::1-4, Pax-4, SREBP, TATA	2b

Data are shown for demonstrating evidence of histone marks, DNAse hypersensitivity sites or transcription factor occupancy of the GWS SNPs

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using HaploReg v4.1. [a]the RegulomeDB score represent: 1a, eQTL + TF binding + matched TF motif + matched DNase Footprint + DNase peak; 1b, eQTL + TF binding + any motif + DNase Footprint + DNase peak; 1c, eQTL + TF binding + matched TF motif + DNase peak; 1d, eQTL + TF binding + any motif + DNase peak; 1e, eQTL + TF binding + matched TF motif; 1f, eQTL + TF binding / DNase peak; 2a, TF binding + matched TF motif + matched DNase Footprint + DNase peak; 2b, TF binding + any motif + DNase Footprint + DNase peak; 2c, TF binding + matched TF motif + DNase peak

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Table S4. EQTL analysis for rs9268832 and rs3115628 from the GTEx2015_v6 study

SNP	Correlated gene	p-value	Tissue
rs9268832	*HLA-DRB6*	4.88E-37	Muscle_Skeletal
rs9268832	*HLA-DRB6*	5.78E-37	Whole_Blood
rs9268832	*HLA-DRB6*	9.02E-34	Lung
rs9268832	*HLA-DRB6*	5.39E-33	Adipose_Subcutaneous
rs9268832	*HLA-DRB6*	1.91E-31	Artery_Tibial
rs9268832	*HLA-DRB6*	2.49E-28	Thyroid
rs9268832	*HLA-DRB6*	2.60E-28	Skin_Sun_Exposed_Lower_leg
rs9268832	*HLA-DRB6*	4.27E-28	Nerve_Tibial
rs9268832	*HLA-DRB6*	7.06E-21	Skin_Not_Sun_Exposed_Suprapubic
rs9268832	*HLA-DRB6*	1.14E-20	Heart_Left_Ventricle
rs9268832	*HLA-DRB6*	2.07E-20	Esophagus_Muscularis
rs9268832	*HLA-DRB6*	4.59E-20	Artery_Aorta
rs9268832	*HLA-DRB6*	1.23E-19	Esophagus_Mucosa
rs9268832	*HLA-DQA2*	1.57E-19	Whole_Blood
rs9268832	*HLA-DRB6*	1.57E-17	Testis
rs9268832	*HLA-DRB6*	1.66E-17	Breast_Mammary_Tissue
rs9268832	*HLA-DRB1*	1.27E-16	Whole_Blood
rs9268832	*HLA-DRB6*	2.23E-16	Stomach
rs9268832	*HLA-DRB6*	3.60E-16	Adipose_Visceral_Omentum
rs9268832	*HLA-DRB6*	6.63E-15	Colon_Transverse
rs9268832	*HLA-DQB1*	1.11E-14	Whole_Blood
rs9268832	*HLA-DRB6*	1.61E-14	Heart_Atrial_Appendage
rs9268832	*HLA-DQA2*	2.25E-14	Muscle_Skeletal
rs9268832	*HLA-DQB1*	2.37E-14	Artery_Tibial
rs9268832	*HLA-DRB6*	4.52E-14	Esophagus_Gastroesophageal_Junction
rs9268832	*HLA-DRB6*	1.09E-13	Cells_EBV-transformed_lymphocytes
rs9268832	*HLA-DQA2*	2.09E-13	Adipose_Subcutaneous
rs9268832	*XXbac-BPG254F23.6*	4.26E-13	Whole_Blood
rs9268832	*XXbac-BPG254F23.6*	7.15E-13	Skin_Sun_Exposed_Lower_leg
rs9268832	*HLA-DRB6*	8.30E-13	Adrenal_Gland
rs9268832	*HLA-DRB6*	8.75E-13	Pancreas
rs9268832	*HLA-DRB6*	3.01E-12	Prostate
rs9268832	*HLA-DRB6*	3.86E-12	Artery_Coronary
rs9268832	*HLA-DRB6*	5.14E-12	Small_Intestine_Terminal_Ileum
rs9268832	*HLA-DQB1*	5.91E-12	Skin_Sun_Exposed_Lower_leg
rs9268832	*HLA-DRB6*	7.95E-12	Colon_Sigmoid
rs9268832	*XXbac-BPG254F23.6*	8.64E-12	Nerve_Tibial
rs9268832	*HLA-DQB1*	1.16E-11	Muscle_Skeletal
rs9268832	*HLA-DQB1*	1.56E-11	Lung
rs9268832	*HLA-DQA2*	2.76E-11	Artery_Tibial
rs9268832	*HLA-DRB1*	3.33E-11	Lung
rs9268832	*XXbac-BPG254F23.6*	3.55E-11	Skin_Not_Sun_Exposed_Suprapubic
rs9268832	*HLA-DQB1*	3.97E-11	Adipose_Subcutaneous

SNP	Correlated gene	p-value	Tissue
rs9268832	*XXbac-BPG254F23.6*	5.48E-11	Adipose_Subcutaneous
rs9268832	*HLA-DRB1*	6.90E-11	Artery_Tibial
rs9268832	*HLA-DRB6*	1.05E-10	Pituitary
rs9268832	*XXbac-BPG254F23.6*	1.66E-10	Lung
rs9268832	*HLA-DRB1*	1.73E-10	Skin_Sun_Exposed_Lower_leg
rs9268832	*XXbac-BPG254F23.6*	2.48E-10	Thyroid
rs9268832	*HLA-DRB1*	3.30E-10	Muscle_Skeletal
rs9268832	*HLA-DQA2*	4.81E-10	Lung
rs9268832	*HLA-DRB1*	7.40E-10	Esophagus_Mucosa
rs9268832	*XXbac-BPG254F23.6*	8.37E-10	Breast_Mammary_Tissue
rs9268832	*HLA-DQB1*	9.80E-10	Thyroid
rs9268832	*HLA-DQB1*	1.01E-09	Nerve_Tibial
rs9268832	*HLA-DRB1*	3.54E-09	Adipose_Subcutaneous
rs9268832	*HLA-DQB1-AS1*	4.44E-09	Adipose_Subcutaneous
rs9268832	*XXbac-BPG254F23.6*	6.46E-09	Artery_Tibial
rs9268832	*HLA-DQB1*	9.58E-09	Esophagus_Mucosa
rs9268832	*HLA-DRB6*	1.05E-08	Spleen
rs9268832	*HLA-DQB1-AS1*	1.18E-08	Skin_Sun_Exposed_Lower_leg
rs9268832	*HLA-DRB1*	1.19E-08	Testis
rs9268832	*HLA-DQA2*	1.63E-08	Nerve_Tibial
rs9268832	*HLA-DQB1*	1.79E-08	Testis
rs9268832	*HLA-DRB6*	2.01E-08	Liver
rs9268832	*HLA-DRB1*	2.91E-08	Colon_Transverse
rs9268832	*HLA-DQA2*	3.33E-08	Colon_Transverse
rs9268832	*HLA-DRB6*	3.75E-08	Brain_Cerebellum
rs9268832	*HLA-DRB1*	3.84E-08	Nerve_Tibial
rs9268832	*HLA-DQA2*	4.39E-08	Breast_Mammary_Tissue
rs3115628	*HCG4P5*	6.37E-24	Adipose_Subcutaneous
rs3115628	*HCG4P5*	2.00E-23	Whole_Blood
rs3115628	*HCG4P5*	9.92E-19	Skin_Sun_Exposed_Lower_leg
rs3115628	*HCG4P5*	6.01E-17	Muscle_Skeletal
rs3115628	*HCG4P5*	3.41E-16	Skin_Not_Sun_Exposed_Suprapubic
rs3115628	*HCG4P5*	9.86E-15	Esophagus_Mucosa
rs3115628	*HCG4P5*	3.00E-14	Lung
rs3115628	*HCG4P5*	1.06E-13	Thyroid
rs3115628	*HCG4P5*	4.55E-13	Nerve_Tibial
rs3115628	*HLA-J*	1.03E-12	Adipose_Subcutaneous
rs3115628	*HLA-J*	1.35E-12	Thyroid
rs3115628	*HCG4P5*	1.92E-12	Artery_Tibial
rs3115628	*HCG4P5*	4.10E-12	Cells_Transformed_fibroblasts
rs3115628	*HLA-J*	8.98E-12	Nerve_Tibial
rs3115628	*HCG4P5*	1.28E-11	Adipose_Visceral_Omentum
rs3115628	*HCG4P5*	2.88E-11	Breast_Mammary_Tissue
rs3115628	*HCG4P5*	3.00E-11	Esophagus_Muscularis
rs3115628	*HLA-J*	1.90E-10	Artery_Tibial

SNP	Correlated gene	p-value	Tissue
rs3115628	*HLA-K*	2.42E-10	Brain_Frontal_Cortex_BA9
rs3115628	*HLA-K*	2.60E-10	Testis
rs3115628	*HCG4P5*	5.07E-10	Colon_Transverse
rs3115628	*HLA-H*	5.09E-10	Cells_Transformed_fibroblasts
rs3115628	*HLA-K*	5.96E-10	Skin_Sun_Exposed_Lower_leg
rs3115628	*HLA-J*	8.80E-10	Muscle_Skeletal
rs3115628	*HCG4P5*	1.38E-09	Esophagus_Gastroesophageal_Junction
rs3115628	*HLA-K*	1.56E-09	Esophagus_Mucosa
rs3115628	*HLA-J*	2.16E-09	Whole_Blood
rs3115628	*ZFP57*	2.38E-09	Thyroid
rs3115628	*HLA-H*	4.40E-09	Brain_Cerebellum
rs3115628	*ZFP57*	4.84E-09	Artery_Aorta
rs3115628	*ZFP57*	7.38E-09	Muscle_Skeletal
rs3115628	*HLA-H*	7.62E-09	Artery_Tibial
rs3115628	*HLA-J*	8.38E-09	Skin_Sun_Exposed_Lower_leg
rs3115628	*HCG4P5*	1.84E-08	Stomach
rs3115628	*ZFP57*	3.08E-08	Esophagus_Mucosa
rs3115628	*HLA-H*	4.56E-08	Skin_Sun_Exposed_Lower_leg

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Table S5. Pair-wise LD analysis (r^2) of the AOSD and JIA associated SNPs within the HLA region

		rs3094178	**rs9268791**	**rs2395148**	**rs41291794**	**rs7775055**
AOSD associated SNP	**rs3094178**	-	0.020	0.030	0.000	0.001
AOSD associated SNP	**rs9268791**	0.020	-	0.053	0.031	0.002
JIA associated SNP	**rs2395148**	0.030	0.053	-	0.011	0.003
JIA associated SNP	**rs41291794**	0.000	0.031	0.011	-	0.004
JIA associated SNP	**rs7775055**	0.001	0.002	0.003	0.004	-

The r^2 metrics were estimated based on our data set using PLINK.

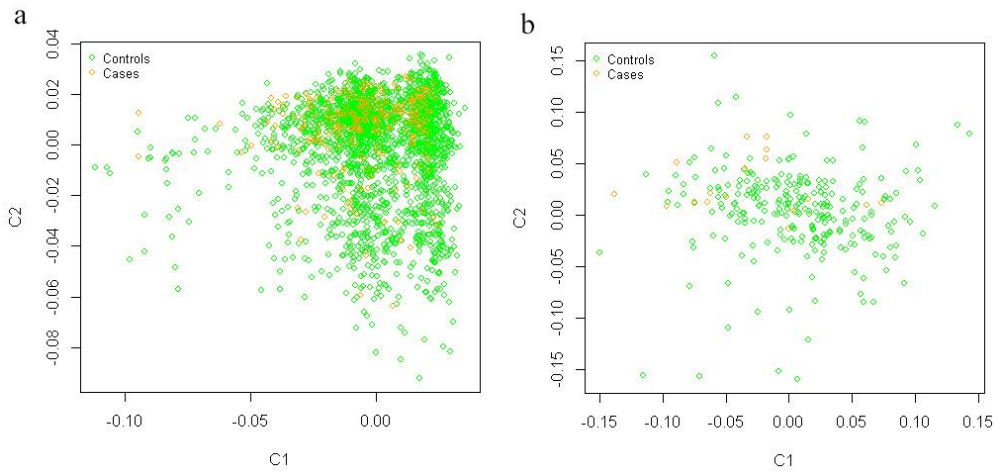

Figure S1. Plot of the first two principal components from principal components analysis of our sample. a) discovery: 247 cases versus 2,163 controls; b) replication: 17 cases versus 257 controls. The first principal component (C1, x axis) was plotted against the second principal component (C2, y axis). Controls are green circles and Cases are yellow circles.

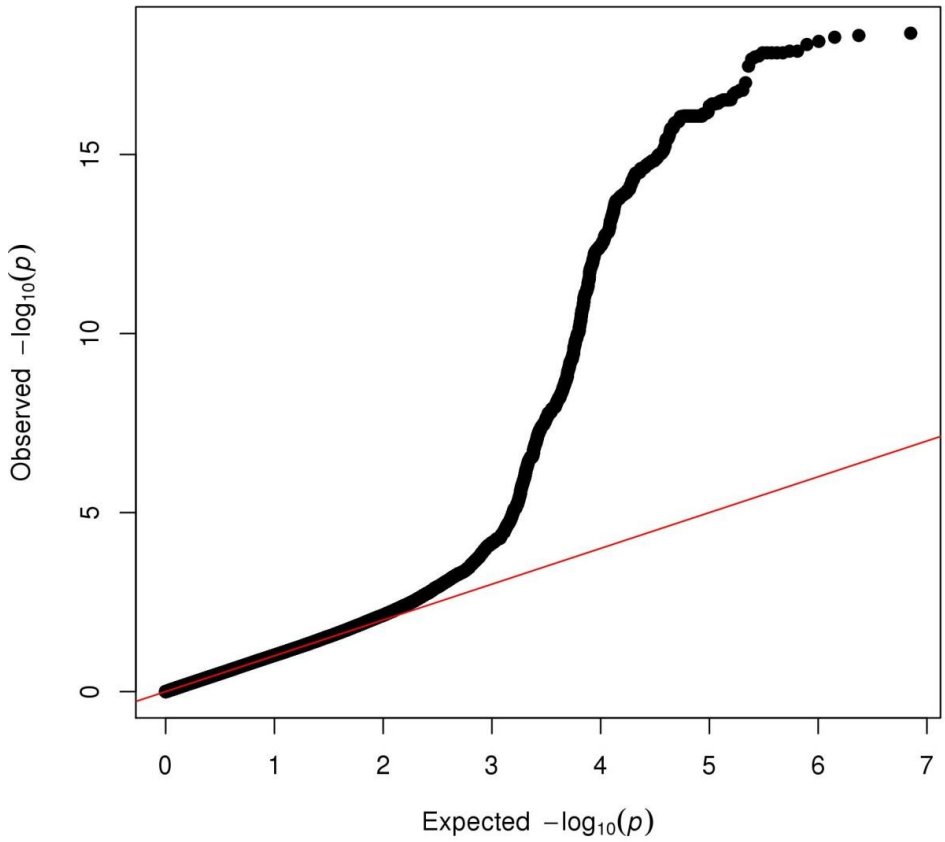

Figure S2. Quantile-quantile (Q-Q) plot of the GWAS analysis. The Q-Q plot representative of observed (y axis) vs. expected (x axis) SNP p values distribution. Expected p values are those expected under the null hypothesis, and the uniform null distribution is marked with a red line.

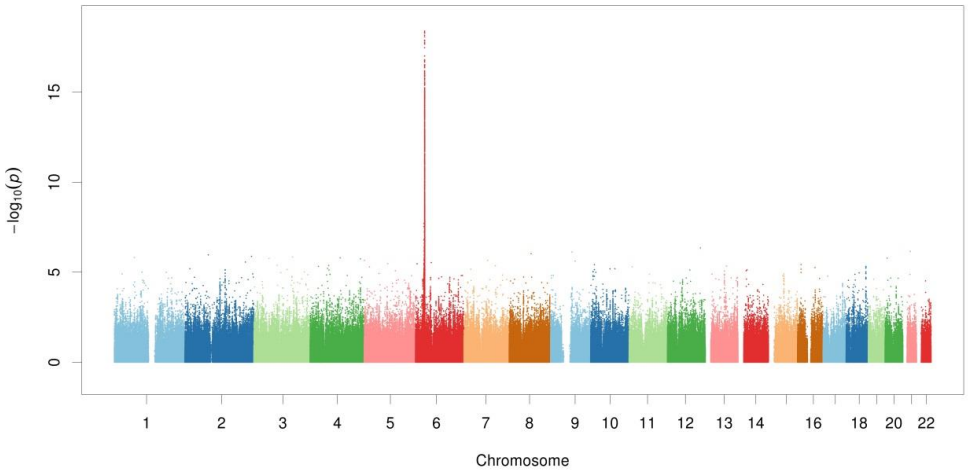

Figure S3. Manhattan plot of the GWAS analysis. Genome-wide P-values ($-\log_{10}p$, y axis) plotted against their respective chromosomal positions (x axis).

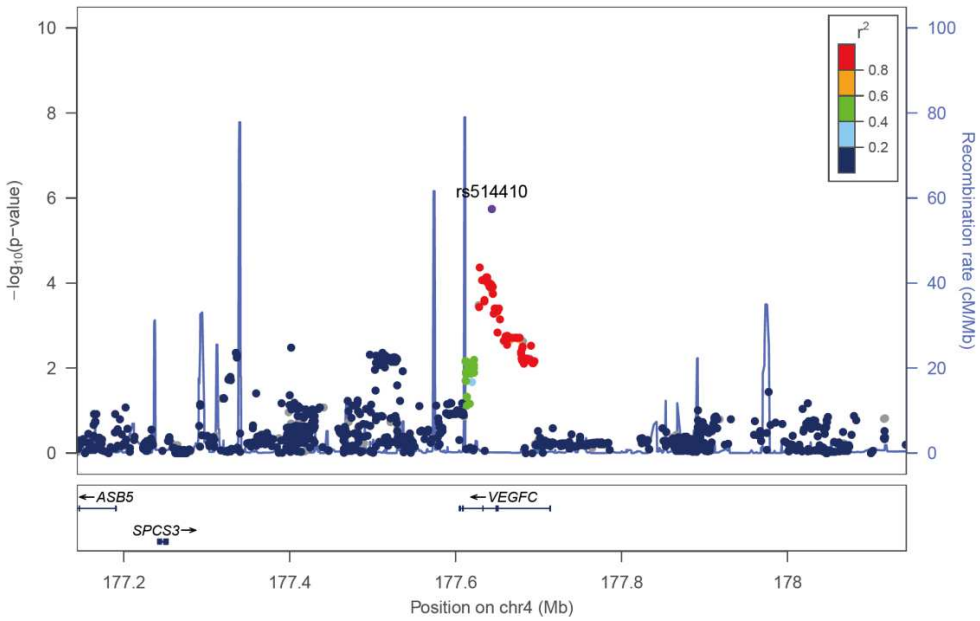

Figure S4. Regional association plot of the VEGFC region. Purple circles represent the most significantly associated SNPs (marker SNPs) in each region in the meta-analysis of discovery and replication. -log10p values (y axis) of the SNPs (within the regions spanning 500 kb on either side of the marker SNP) are presented according to the chromosomal positions of the SNPs (x axis, hg19). SNPs are colored according to their linkage disequilibrium (LD) with the marker SNP. The LD values were established based on the 1000 Genomes Asian (ASI) data (March 2012). Estimated recombination rates with samples from the 1000 Genomes Project March 2012 release are shown as blue lines, and the genomic locations of genes within the regions of interest annotated from the UCSC Genome Browser are shown as arrows.

Supplementary Methods

Participants

The clinical samples and information of Chinese AOSD patients were collected from several different centers/hospitals in China. For all cases, the clinical manifestations, laboratory testing, treatment response and follow-up were evaluated by rheumatologists from each collaborative center/hospital, and senior rheumatologists of Rui'jin Hospital re-evaluated the diagnoses and then ultimately pooled them in the database. All the included AOSD patients fulfilled Yamaguchi's diagnostic criteria[1]. The controls were healthy individuals recruited from the physical examination centers of the collaborative hospitals. After quality control (QC), this study included 264 AOSD cases and 2,420 geographically and ethnically matched healthy controls (discovery: 247 cases versus 2,163 controls, recruited from northern and central China; replication: 17 cases versus 257 controls, recruited from southern China). 64% of cases were female and the average age of onset was 35.6 years old. All samples were collected from AOSD patients at onset. The study was approved by the institution's ethics committees, and all participants signed informed written consent forms. Approval (Rui'jin Hospital Ethics Committee, 2016(62)) was received for our study from the local Ethics Committee of Human Genetic Resources.

DNA extraction

EDTA-anticoagulated venous blood samples were collected from all participants. Genomic DNA was extracted from peripheral blood monocytes using FlexiGene DNA kits and was diluted to a working concentration of 50 ng/μl for array genotyping.

GWAS genotyping and quality control

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The genome-wide scan was performed using the Illumina Infinium Global Screening Array-24 v1.0 BeadChip. A total of 2,721 chips data were generated, and the genotyping data and inferred gender were generated using Illumina's GenomeStudio v2.0.2. Seven pairs of randomly selected sample replications were used to test reproducibility and yielded concordance rates >99% for all pairs. For each pair, only the one with the higher call rate was retained for further analysis. Before conducting the association analysis, systematic quality control analyses were performed at both the sample and single-nucleotide polymorphism (SNP) levels as follows: for the sample QC, (i) individuals had a discrepancy between the documented gender and the inferred gender based on genotyping data (n=3); (ii) heterozygosity rates were calculated, and deviations of more than 6 s.d. from the mean were excluded (n=0); (iii) identity-by-descent analysis was performed with PLINK[2], and the member (with a lower call rate) of the pair of unexpected duplicates or probable relatives (PI_HAT>0.25) was also excluded (n=12); and (iv) population outliers from principal component analysis (PCA) were removed (n=15). For the SNP QC, SNPs with the following characteristics were excluded: (i) had a call rate of <98% (n= 87,374); (ii) had minor allele frequencies (MAFs) <0.01 (n=299,180); (iii) had a genotype distribution in the controls that deviated from the expected Hardy-Weinberg equilibrium (HWE $p<1.0\times10^{-6}$, n=31,856); or (iv) for SNPs with $p<1\times10^{-4}$, failed genotyping assessed by visual inspection of cluster plot (n=1,906). After QC, a set of 367,536 genotyped SNPs in 264 cases and 2,420 controls remained for further imputation analysis.

Analysis of population substructure

A linkage disequilibrium (LD)-based SNP pruning analysis was performed with

PLINK[2]. Using the LD-pruned autosomal SNPs genotypes, PCAs were conducted to evaluate the population substructure of the sample using EIGENSTRAT software[3]. We also removed population outliers, which were defined as individuals whose ancestry was more than 6 s.d. from the mean on one of the top 10 inferred axes of variation. In this step, 15 outliers were identified and removed.

Imputation analysis of untyped SNPs

The entire genotyped set was imputed as follows: the genotypes were phased using SHAPEIT[4] for each chromosome, and imputation was performed for each 5-Mb chromosome interval using IMPUTE2[5]. The haplotypes derived from the 1000 Genomes Project Phase 3[6] were used as reference data. The variants with INFO>0.8, MAF>0.01, a call rate ≥98% and HWE $p \geq 1 \times 10^{-6}$ in the controls were saved for further analysis. A set of 3,547,931 genetic variants for 264 AOSD cases and 2,420 controls remained in the final analysis.

Statistical methods

For the single variant association analysis, we used logistic regression with PLINK[2]. We performed conditional analysis to test for independent effects of an individual variant using PLINK. Effects from different data sets were combined using meta-analysis under a fixed-effects model with inverse variance weighting. Heterogeneity was assessed using Cochran's Q test, and the I^2 index was used to indicate the degree of heterogeneity. For rs514410, we also adopted the Cochran-Mantel-Haenszel analysis to combined discovery and replication samples[7, 8]. The regulatory and epigenomic annotation of the genome-wide significant SNPs were explored using HaploReg v4.1[9]. RegulomeDB v1.1 were used to assess their

potential functional consequence[10].

Sanger sequencing confirmation

To evaluate and correct possible genotyping or imputation error, we genotyped the three SNPs (rs9268791, rs3094178 and rs514410) using Sanger sequencing for cases (online supplementary table S1). The genotypes for array genotyping (rs514410) or imputation (rs9268791 and rs3094178) were corrected based on the Sanger sequencing if inconsistent genotypes observed (two cases for rs9268791, four cases for rs3094178, and seven cases for rs514410).

Supplementary Discussion

SNP rs514410 is located within the intron of *VEGFC*. The *VEGFC* gene encodes vascular endothelial growth factor-C (VEGF-C). VEGF-C plays a crucial role in the development of lymphatic vessels and lymphangiogenesis[11]. VEGF-C also promotes the migration of mesenchymal stem cells and immune cells[12, 13], which are known to play key roles in the immune response. AOSD patients usually show lymphadenopathy, splenomegaly and proliferation of bone marrow cells and synovial tissue[14]. This kind of acute proliferation at onset might be triggered by abnormal stimulatory cytokine release and related uncontrolled response or signaling pathway activation. VEGF-C was involved in the maintenance of interferon-related immune balance[15]. In addition, VEGF-C signaling plays a key role in regulating toll-like receptor 4 (TLR4)-triggered inflammation in macrophages. In AOSD patients, the endogenous TLR4 ligand S100A8/A9 levels were significantly elevated and correlated with disease activity[16]. The innate immune processes involving S100A8/A9 have an important role in the pathogenesis of AOSD[16]. This evidence

indicated pleiotropy and multifunctionality for VEGF-C, and suggested their functional relevance for AOSD.

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Abbreviations List

AOSD, Adult-Onset Still's Disease;

JIA, juvenile idiopathic arthritis;

HLA, human leukocyte antigen;

VEGF-C, vascular endothelial growth factor-C;

GWS, genome-wide significance;

OR, odds ratio;

GWAS, genome-wide association study;

eQTL, expression quantitative trait loci;

EDTA, ethylenediaminetetraacetic acid;

QC, quality control;

PCA, principal component analysis;

SNP, single-nucleotide polymorphism;

LD, linkage disequilibrium;

HWE, Hardy-Weinberg equilibrium;

MAF, minor allele frequency;

TLR4, toll-like receptor 4;

Q-Q, Quantile-quantile.

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