frontiers | Frontiers in Ophthalmology

REVIEW
published: 03 June 2022
doi: 10.3389/fopht.2022.916887

Genetics in Behcet's Disease: An Update Review

*Yu Gao, Zhenyu Zhong and Peizeng Yang**

The First Affiliated Hospital of Chongqing Medical University, Chongqing Key Laboratory of Ophthalmology, Chongqing Eye Institute, and Chongqing Branch of National Clinical Research Center for Ocular Diseases, Chongqing, China

Behcet's disease (BD) is one of the most vision-threatening clinical entities of uveitis. Although the etiopathogenesis of BD remains obscure, accumulating evidence has demonstrated that both genetic and environmental factors may contribute to the development of BD. Genome-wide association studies (GWAS) and candidate association studies have identified several genetic variants strongly associated with BD, including variants in human leukocyte antigen (HLA) -A02, -A03, -A24, -A26, -A31, -B15, -B27, -B35, -B49, -B51, -B57, -B58, -C0704, CIITA, ERAP1, MICA, IL1A-IL1B, IL10, IL12, IL23R, IL-23R/IL-12RB2, IL1RL1-IL18R1, STAT4, TFCP2L1, TRAF5, TNFAIP3, CCR1/CCR3, RIPK2, ADO-ZNF365-EGR2, KLRC4, LACC1, MEFV, IRF8, FUT2, CEBPB-PTPN1, ZMIZ1, RPS6KA4, IL10RA, SIPA1-FIBP-FOSL1, VAMP1, JRKL/CTCN5, IFNGR1 and miRNA-146a. Epigenetic modifications are also reported to play essential roles in the development of BD, including DNA methylation and histone modification. We review here the recent advances in the genetic and epigenetic factors associated with the BD pathogenesis.

Keywords: Behcet's disease, genetics, single nucleotide polymorphism, copy number variation, epigenetic modification

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***Correspondence:**
Peizeng Yang
peizengycmu@126.com

Specialty section:
This article was submitted to Inflammatory Eye Diseases, a section of the journal Frontiers in Ophthalmology

Received: *10 April 2022*
Accepted: *04 May 2022*
Published: *03 June 2022*

Citation:
Gao Y, Zhong Z and Yang P (2022) Genetics in Behcet's Disease: An Update Review. Front. Ophthalmol. 2:916887. doi: 10.3389/fopht.2022.916887

INTRODUCTION

Uveitis is a group of inflammatory ocular diseases affecting the uveal tract, retina, and retinal blood vessels. It constitutes a number of visual impairments worldwide. Behcet's disease (BD) is one of the most vision-threatening entities of uveitis. BD patients account for 16.5% of the total uveitis patients according to a Chinese study (1). BD is an autoinflammatory disorder that affects multiple systems, characterized by intraocular inflammation, arthritis, oral and genital ulcers and skin damages (2). While young adults aged 20-40 years are the commonest age group affected by BD, it still can be seen in children and older patients (3). Young male patients are reported to be affected more frequently and more severely than female patients (4). BD affects millions of people worldwide but mainly occurs along the 'silk road', with a higher incidence in Turkey, China, Japan and Iran, and a lower incidence in Europe and North America (5).

Approximately 70% of BD patients suffer from ocular involvement and the most common ocular finding is uveitis (6). BD patients with uveitis usually display recurrent and refractory ocular involvement, leading to severe visual impairments even blindness. However, the pathogenesis of BD is not entirely understood. Currently, genetic and environmental factors are considered to be responsible for the development of BD. A previous study comprising 21,940,795 individuals in

12 million families in Korea demonstrated that the familial incidence and risk of BD increased a lot among first degree relatives, especially in individuals with an affected twin (165-fold) (7). As a growing number of studies focus on the genetic predisposition for BD, multiple genetic variants associated with BD have been identified (8). Particularly, susceptibility gene for BD can be divided into human leucocyte antigen (HLA) and non-HLA. Identified genetic variants for BD include single nucleotide polymorphisms (SNPs) (**Table 1**) and copy number variations (CNVs) (**Table 2**), with variants ranging from single base to large fragment changes. Epigenetic modifications are also reported to be important in the development of BD, including DNA methylation and histone modification (62). The present review aims to summarize the latest genetic and epigenetic progress on BD.

VARIANTS IN HUMAN LEUCOCYTE ANTIGEN AND ITS RELATED GENES

HLA is located on the chromosome 6p21.3 and functions to encode various important proteins of immune responses. HLA antigen plays a critical role in self/nonself-discrimination by presenting antigens to T cells and eliminating pathogenic microorganisms such as bacteria and viruses (63). Multiple HLA alleles have been identified to be associated with various autoimmune diseases, especially BD in different populations. HLA-A02, -A24, -A26, -A31, -B27, -B51, -B57 were considered to be BD-risk alleles, while HLA-A03, -B15, -B35, -B49, -B58 were thought to be BD-protective (15, 37, 64, 65). HLA-B51 has been recognized as the most significant susceptibility gene for BD in a large number of GWAS and candidate association studies, and it was carried in about 60% of BD patients (22, 41, 66, 67). Moreover, HLA-B51 carriers were more prone to developing ocular manifestations of BD, which was observed towards the east along the Silk Road in Eurasia rather than west-Eurasian (68). However, HLA-B51 was only responsible for 19% of the genetic susceptibility to BD (69). Recently, we discovered HLA-C0704 to be associated with BD in a GWAS study involving a Chinese Han population, including eight independent SNPs at the genome-wide level (52).

Meanwhile, multiple HLA-related gene variants also play essential roles in BD, including variants in the class II major histocompatibility complex transactivator (CIITA), endoplasmic Reticulum Aminopeptidase 1 (ERAP1) and the major histocompatibility complex class I chain related gene A (MICA) (64). CIITA is an important transcriptional coactivator that modulates expression of MHC class II genes, IL-4 and IL-10 (70). In a Chinese Han population, the CIITA SNP rs12932187 G allele and GG genotype were identified to be involved in BD (40). The expression of CIITA was increased while that of IL-10 was decreased in peripheral blood monocytes (PBMC) stimulated by Lipopolysaccharide (LPS) of GG carriers (40).

ERAP1 is an important enzyme that trims peptides for binding onto MHC class I molecules. SNP rs17482078 in ERAP1 was found as a risk factor for BD in a Turkish GWAS and the finding was replicated in Iranian (27, 33). Moreover, SNP rs10050860, rs1065407, rs2287987 and rs2013717 in ERAP1 were also associated with BD in a Chinese GWAS study (52).

MICA is a highly polymorphic non-classic HLA gene that modulates immune responses by binding to its receptors on natural killer (NK) cells, CD8 T cells, and γδT cells (63, 71, 72). The DNA sequence of MICA is highly polymorphic. A tri-nucleotide microsatellite polymorphism (GCT/AGC) n was identified in the MICA transmembrane region designated as An (A4, A5, A5.1, A6, A9) allele (63). Among them, MICA-A6 conferred risk to BD while the rest alleles were thought to be protective, especially in the Middle East and East Asia (71, 73). MICA*009 and MICA* 019 were identified as risk alleles for BD involving a Spanish population (71, 74). However, a recent study in a Han Chinese population showed that no significant difference of MICA*009 polymorphisms were observed between the BD patients and controls, which indicated genetic heterogeneity of MICA gene polymorphisms in different populations (75). Additionally, MICA*049 was firstly reported to have an association with BD in this study, and this association was suggested to be independent from that with HLA-B51. The MICA*009 allele was probably mixed with the MICA*049 allele previously, since the only difference between the MICA*00901 (a subtype of MICA*009) and the MICA*049 existed at codon 335 in exon 6 which was not studied. The MICA*009 was distinguished from the MICA*049 by T-ARMS-PCR in this study (75). Consistent with previous studies, the MICA*A6 was strongly associated with BD Chinese population.

SINGLE NUCLEOTIDE POLYMORPHISMS IN INTERLEUKIN FAMILY GENES

Interleukin-10 (IL-10) is a widely expressed cytokine that contributes to preventing inflammatory and autoimmune pathologies. Multiple cells of innate and adaptive immune system exert important functions in BD, including $CD4^+$T cells (76, 77), $CD8^+$ T cells (78), dendritic cells (79), macrophages (80), NK cells (81), neutrophils (82) and B cells (83, 84), and almost all of them could express IL-10 (85). IL-10 was identified as risk locus for many inflammatory diseases, including bacterial sepsis (86), type I diabetes (87), mixed connective tissue disease (MCTD) (88), ankylosing spondylitis (AS) (89) and especially BD (9, 11, 12, 90).

Multiple SNPs of IL-10 were confirmed to be strongly associated with BD. Residing in the intron 3 of IL-10, the SNP rs1554286 was highly associated with BD in Japanese populations (12). A meta-analysis of IL-10 with additional studies in Turkish and Korean cohorts identified that IL-10 locus rs1800872 ($P=2.1\times10^{-14}$) and rs1800871 ($P=1.0\times10^{-14}$) had genome-wide significant associations with BD (12). Association between rs1518111 polymorphism of IL-10 and risk of BD was identified by multiple studies in various populations (11, 27, 30, 34). A recent GWAS study of Chinese BD uveitis involving 978 patients and, 4388 controls also

TABLE 1 | Summary HLA types and non-HLA SNPs associated with Behcet's disease.

Year	Gene	SNP	P value	Risk Allele/Genotype	OR	non-risk Allele/Genotype	Method	Reference
2009	LOC100129342	rs11206377	3.00E-04	G	1.84	A	GWAS	(9)
	KIAA1529	rs2061634	4.20E-05	G	2.04	A		
	CPVL	rs317711	1.00E-04	C	2.26	T		
	UBASH3B	rs4936742	1.50E-03	T	1.71	C		
	UBAC2	rs9513584	5.80E-03	G	1.61	A		
2009	UBAC2	rs9517668	3.61E-05	T	2.62	C	Candidate	(10)
		rs9554581	8.53E-05	T	2.48	C		
		rs9517644	1.30E-03	T	1.72	C		
		rs11069357	2.00E-03	A	1.68	G		
		rs984477	4.30E-03	G	1.65	A		
		rs9513584	1.70E-03	G	1.74	A		
		rs9554573	1.20E-03	A	1.73	G		
		rs6491493	1.10E-03	G	1.74	A		
		rs7999348	5.80E-04	G	1.78	A		
		rs17575643	1.80E-04	T	2.91	C		
		rs727263	1.00E-04	A	2.45	G		
		rs7332161	1.10E-04	A	2.43	G		
		rs912130	7.10E-03	G	1.58	A		
		rs2892976	2.30E-04	G	1.96	A		
2010	IL10	rs1518111	1.88E-08	A	1.41	G	GWAS	(11)
	IL23R-IL12RB2	rs924080	5.35E-06	A	1.31	G		
	CPLX1	rs11248047	1.26E-07	G	1.36	A		
2010	IL23R-IL12RB2	rs1495965	1.90E-11	G	1.35	A	GWAS	(12)
	IL10	rs1800872	2.10E-14	A	1.45	G		
		rs1800871	1.00E-14	T	1.45	C		
2010	STAT4	rs7574865	9.00E-03	GG	1.61	TT/GT	Candidate	(13)
2010	IL23R	rs17375018	8.88E-04	G	1.57	A	Candidate	(14)
			3.47E-04	GG	1.86	AA/AG		
		rs11209032	1.26E-03	A	1.48	G		
			2.40E-02	AA	1.69	AG/GG		
2010	HLA	HLA-A2601	5.29E-03	–	3.56	–		(15)
2010	MICA	rs2523467	2.30E-09	A	0.59	G	GWAS	(16)
		rs3094584	4.70E-10	T	1.69	C		
2011	FCRL3	rs11264799	4.40E-02	C	1.43	A	Candidate	(17)
2012	STAT3	rs2293152	2.10E-02	GG	1.71	CC/CG	Candidate	(18)
2012	TGFBR3	rs1805110	3.00E-02	CC	0.62	CT/TT	Candidate	(19)
2012	UBAC2	rs3825427	6.90E-06	T	1.50	C	Candidate	(20)
		rs9517668	3.30E-04	T	1.40	C		
		rs9517701	2.90E-05	G	1.40	A		
2012	IL10	rs1518111	2.53E-02	T	1.20	C	Candidate	(21)
	IL23R–IL12RB2	rs17375018	1.93E-06	G	1.51	A		
		rs7517847	1.23E-06	T	1.48	C		
		rs924080	1.78E-05	T	1.29	C		
		rs10489629	7.00E-04	–	1.30	–		
		rs1343151	2.00E-04	–	1.39	–		
		rs1495965	1.00E-04	–	1.33	–		
2012	STAT4	rs7574070	3.36E-07	T	1.40	C	GWAS	(22)
		rs7572482	1.30E-08	T	1.44	C		
		rs897200	6.20E-09	A	1.45	G		
	TFCP2L1	rs17006292	5.16E-09	G	4.17	A		
2012	CD40	rs4810485	6.00E-03	TT	1.98	GG/GT	Candidate	(23)
		rs1883832	1.20E-02	TT	1.73	CC/CT		
2012	CCR1/CCR3	rs13084057	1.71E–7	A	3.13	G	Candidate	(24)
		rs13092160	6.50E-08	T	3.57	C		
		rs13075270	2.76E-07	T	3.13	C		
2012	PDGFRL	rs17633132	5.20E-03	C	2.33	T	Candidate	(25)
2013	TNFAIP3	rs9494885	8.35E-10	C	1.81	T	Candidate	(26)
			1.83E-10	TC	2.03	CC/TT		
		rs10499194	5.00E-03	C	1.92	T		
			1.50E-02	CC	1.96	TC		
		rs7753873	2.50E-02	C	1.39	A		
			1.50E-02	AC	1.49	AA		
2013	CCR1-CCR3	rs7616215	4.30E-13	C	1.39	T	GWAS	(27)

(Continued)

TABLE 1 | Continued

Year	Gene	SNP	P value	Risk Allele/Genotype	OR	non-risk Allele/Genotype	Method	Reference
	STAT4	rs7574070	1.29E-09	A	1.27	C		
	KLRC4	rs2617170	1.34E-09	T	1.28	C		
	IL12A	rs17810546	6.01E-07	A	1.55	G		
	ERAP1	rs17482078	4.73E-11	TT	4.56	CC/CT		
2013	MEFV	rs61752717	1.79E-12	M694V	2.65	–	Candidate	(28)
2013	IL23R	rs17375018	1.00E-02	G	1.37	A	Candidate	(29)
		rs7517847	1.00E-04	T	1.59	G		
		rs1343151	1.00E-02	G	1.36	A		
	IL10	rs2222202	1.00E-02	G	1.35	A		
2014	IL10	rs1800871	2.40E-02	T	1.30	C	Candidate	(30)
		rs1518111	2.60E-02	A	1.30	G		
2014	TRAF5	rs12569232	1.30E-03	G	1.48	C	Candidate	(31)
		rs6540679	1.16E-10	A	1.59	G		
	TRAFIP2	rs13210247	2.07E-07	G	2.40	A		
2015	IFI16	rs7532207	4.70E-02	T	1.41	C	Candidate	(32)
		rs6940	4.00E-02	T	1.42	C		
	AIM2	rs855873	3.10E-02	G	1.52	A		
2015	CCR1	rs7616215	5.05E-09	T	1.52	C	Candidate	(33)
	KLRC4	rs2617170	7.98E-07	C	1.41	T		
	IL12A-AS1	rs17810546	5.96E-06	G	1.92	A		
	STAT4	rs7574070	1.28E-03	A	1.24	G		
	ERAP1	rs10050860	6.96E-03	T	1.32	C		
		rs13154629	7.55E-03	T	1.32	C		
2015	MICA	MICA-A5	8.00E-03	–	–	–	Candidate	(34)
		MICA-A5.1	1.50E-02	–	–	–		
		MICA-A6	1.58E-13	–	2.08	–		
	HLA	HLA-B*51	6.21E-14	–	3.38	–		
	HLA-F-AS1	rs114854070	1.45E-04	T	1.67	C		
	PSORS1C1	rs12525170	2.82E-18	A	3.20	G		
	HLA-B-MICA	rs76546355	4.79E-34	A	4.05	G		
2015	IL12	rs17810456	9.31E-06	G	2.06	A	GWAS	(35)
2015	–	rs7528842	8.62E-04	G	1.35	A	GWAS	(36)
	FUT2	rs632111	2.09E-05	G	1.32	A		
2016	HLA	HLA-A26	4.10E-02	–	3.52	–	Candidate	(37)
		HLA-A31	5.00E-03	–	7.17	–		
		HLA-B51	1.00E-04	–	3.63	–		
2016	TNFSF4	rs1234315	5.91E-03	T	1.48	C	Candidate	(38)
2016	IL-37	rs3811047	1.60E-09	G	1.58	A	Candidate	(39)
	IL-18RAP	rs2058660	1.24E-07	G	1.33	A		
2016	CIITA	rs12932187	6.00E-07	G	1.58	C	Candidate	(40)
	NOD1	rs2075818	6.81E-05	C	1.40	G		
2016	IL12	rs1874886	3.29E-10	A	1.66	G	Candidate	(41)
	JRKL/CNTN5	rs2848479	1.62E-08	A	1.61	G		
	HLA	HLA-B51	6.82E-32	–	3.82	–		
2016	IL23R-IL12RB2	rs924080	2.52E-04	T	1.58	C	Candidate	(42)
		rs11209032	3.46E-04	A	1.45	G		
2017	IL10	rs1800871	3.45E-09	T	1.30	C	Candidate	(43)
		rs3024490	3.98E-07	T	1.32	C		
	IL23R-IL12RB2	rs924080	4.06E-08	T	1.40	C		
		rs12141431	4.00E-09	C	1.34	T		
2017	IL1A-IL1B	rs3783550	2.12E-08	G	1.33	T	Candidate	(44)
	IRF8	rs11117433	2.73E-08	G	1.59	C		
	CEBPB-PTPN1	rs913678	1.96E-09	C	1.33	T		
	IL10	rs1518110	4.55E-09	A	1.34	C		
	CCR1	rs7616215	9.60E-11	T	1.39	C		
	IL12A	rs17753641	1.45E-09	G	1.90	A		
2017	IL23R–IL12RB2	rs4655535	3.30E-05	G	1.40	A	Candidate	(45)
		rs1495966	3.80E-05	T	1.40	C		
		rs1495965	4.90E-05	C	1.40	T		
		rs6665569	4.70E-02	T	1.40	C		
2017	TNFSF4	rs1234313	1.80E-02	A	1.40	G	Candidate	(46)
	TNFSF15	rs4246905	1.37E-05	T	1.58	C		
	TNFSF8	rs7028891	2.80E-02	G	1.36	A		

(Continued)

TABLE 1 | Continued

Year	Gene	SNP	P value	Risk Allele/Genotype	OR	non-risk Allele/Genotype	Method	Reference
2017	CEBPB-PTPN1	rs913678	2.09E-16	C	1.31	T	Candidate	(47)
	LACC1	rs9316059	2.96E-16	A	1.40	T		
	RIPK2	rs10094579	9.21E-11	A	1.32	C		
	ADO-EGR2	rs224127	5.28E-13	A	1.27	G		
2018	FCGR3A	rs428888	7.22E–7	T	1.80	C	Candidate	(48)
			1.96E–07	CT	1.90	CC		
2020	IL1RL1–IL18R1	rs12987977	2.60E-03	T	1.29	G	Candidate	(49)
			8.93E-07	GT/TT	–	GG		
		rs12999364	1.13E-02	C	1.26	T		
			3.15E-04	CC/CT	–	TT		
		rs4851569	9.72E-03	C	1.26	A		
			3.29E-04	CC/CA	–	AA		
2020	IL-27	rs153109	2.00E-02	G	–	A	Candidate	(50)
2020	TNFα	rs1800629	4.24E-02	GA	2.29	GG	Candidate	(51)
2021	HLA	HLA-B51	#######	–	5.86	–	GWAS	(52)
		HLA-A26	9.77E-18	–	2.44	–		
		HLA-C0704	6.07E-17	–	3.78	–		
	IL23R - IL12RB2	rs11209032	1.50E-13	A	1.45	G		
		rs34426521	3.24E-13	G	1.44	A		
		rs12119179	1.83E-12	C	1.43	A		
		rs1495965	5.36E-13	G	1.44	A		
	IL10	rs3021094	5.40E-05	C	1.22	A		
	STAT4	rs7572482	8.90E-06	A	1.25	G		
	ERAP1	rs1065407	8.93E-08	C	1.62	A		
		rs10050860	3.38E-05	A	1.50	G		
		rs2287987	1.66E-05	G	1.52	A		
		rs2013717	2.29E-05	C	1.51	A		
	IFNGR1	rs9376268	4.41E-11	G	1.41	A		
	LACC1	rs3764147	6.71E-14	A	1.54	G		
		rs1373904	1.60E-13	A	1.53	G		
	CEBPB - PTPN1	rs913678	1.72E-05	G	1.27	A		
	RHOH	rs9683756	2.81E-06	A	1.30	G		
	PRDM1	rs13437093	1.14E-08	A	1.33	G		
	MTHFD1L	rs12216229	5.99E-10	A	1.85	G		
	KLF4	rs10733565	8.29E-12	G	1.41	A		
		rs7018799	2.76E-11	G	1.40	A		
		rs10979075	1.36E-12	A	1.43	G		
	ZMIZ1	rs1250569	9.77E-11	A	1.39	G		
	RPS6KA4	rs6591843	9.66E-13	G	1.45	A		
		rs7130280	1.07E-14	G	1.47	A		
	SIPA1-FIBP-FOSL1	rs2448490	5.12E-07	G	1.37	A		
		rs568617	1.10E-05	G	1.25	A		
		rs10791830	1.44E-05	G	1.25	A		
	IL10RA	rs2228054	1.00E-07	G	1.37	A		
		rs2228055	8.81E-08	A	1.37	G		
	VAMP1	rs1034969	4.72E-06	C	1.28	A		
	AGBL1	rs896615	1.91E-05	A	1.27	G		
	CMIP	rs9888833	3.49E-06	A	1.32	G		
	CDH15	rs79831785	5.83E-14	A	2.13	G		
	RNA5SP459-TCF4	rs7237392	4.07E-05	G	1.25	A		
	MRPL39-JAM2	rs2829839	5.62E-05	C	1.27	A		
	GART	rs6517178	6.53E-06	G	1.27	A		
	MIS18A	rs4817467	4.04E-08	A	1.35	G		
2021	IL-35	rs428253	3.40E-02	G	5.00	C	Candidate	(53)
			2.10E-02	GG/GC	–	CC		
2021	IFNGR1	rs4896243	2.42E-09	C	1.25	T	Candidate	(54)
	LNCAROD/DKK1	rs1660760	2.75E-08	C	1.28	T		
2021	miR-146a	rs2910164	2.20E-02	G	1.58	C	Candidate	(55)
	UTS2	rs228648	3.20E-02	Thr	1.60	Met		

GWAS, Genome-wide association studies; OR, Odds ratio; SNP, Single nucleotide polymorphism.

TABLE 2 | Summary CNVs associated with Behcet's disease.

Year	Gene	CNV	P value	OR	Reference
2014	C4	≤2	1.42E-03	–	(56)
		≤4	3.56E-04	–	
2015	TLR7	>2	2.00E-02	–	(57)
2015	C3	>2	2.60E-04	3.4	(58)
	C5	>2	1.50E-05	7.7	
2015	IL17F	>2	4.17E-08	2.2	(59)
	IL23A	>2	2.86E-11	2.8	
2015	Rorc	>2	8.99E-08	3.0	(60)
	Foxp3	<2	1.92E-05	3.1	
2015	FAS	>2	3.35E-08	2.16	(61)

confirmed the risk factor role of the IL-10 variant (rs3021094) (52). In addition, two novel loci of IL10RA (rs2228054 and rs2228055) showed genome-wide significant association with BD uveitis in this study.

Recently, some studies demonstrated how GWAS-identified IL-10 loci contributed to BD progression. IL-10 locus rs1518111 was associated with reduced IL-10 expression, which was a risk factor for BD (11, 12). A previous study proposed that IL-10 loci polymorphism was associated with impaired M2 macrophage (anti-inflammatory) function while promoting M1 macrophage (proinflammatory)-mediated inflammation in BD (91). Our study has identified rs3024490 and rs1800871 of IL-10 as susceptibility loci for BD in Chinese patients. PBMCs of rs3024490/TT genotype carriers showed decreased IL-10 production as compared with GG carriers (43). Interestingly, we further found that the risk allele T of rs3024490, which was located in the enhancer elements of IL-10, may be involved in BD pathogenesis by affecting the binding of TBX1 to IL-10. Since decreased TBX1 expression was shown in BD patients, the binding of TBX1 to IL10 decreased and the expression of IL10 was downregulated. Therefore, the risk of developing BD increased (92). However, whether the genetic changes of TBX1 could directly influence BD remains unknown.

IL-12 is a proinflammatory cytokine which contributes to Th1 activation, NK-cell cytotoxicity and IFNγ production. IL-12 is composed of p40 subunit and p35 subunit. IL-23 is a cytokine that consists of p19 subunit and the common p40 subunit with IL-12. IL-23 functions to influence inflammatory macrophage and memory T cell *via* binding to IL-23 receptor (IL-23R). IL-12 and IL-23 were reported to be involved in autoimmune inflammations (93). A multi-center GWAS study carried out in Western Europeans, Middle Eastern and Turkish, reported the association between IL-12A/rs17810546 with BD (35). Such a finding was replicated in Iranian BD cohorts (33). The locus rs1874886 of IL-12 was found to be a BD susceptibility factor in Spaniards (41). Activation of IL-23/IL-17 pathway is important in many autoinflammatory diseases, including BD (77). IL-12Rβ1 encodes the common subunit of IL23R and IL-12R, while other subunits are encoded by IL23R and IL12RB2 respectively. Stimulated by IL-23 and IL-12, IL-23R and the IL-12RB play important roles in naïve $CD4^+$T cell differentiation and promote the expression of IL-1β, IL-6, IL-17A and TNFα (94). Multiple SNPs (rs12119179, rs4655535, rs924080, rs11209032, rs1343151, rs1495965, rs1495966, rs17375018, rs7517847, rs34426521, 10489629 and rs1966176) located in IL-23R/IL-12RB2 genes were involved in BD in the populations of Turkey (11), Japanese (12), Han Chinese (14, 42, 43), Iranian (21), Korean (45), Spain (29), and Western Algeria (95). However, little is known concerning the specific molecular mechanisms how these gene variants affect the pathogenesis of BD. The specific roles of these identified SNPs are warranted to be explored in further studies.

IL1RL1–IL18R1 region contains a list of genes involved in immune responses, including IL1RL2, IL1RL1, IL18R1, and IL18RAP. These genes contribute to T cells differentiation and cytokine production, such as TNF-α, IL-17A and IL-23 (96–98). Recent studies showed that IL1RL1–IL18R1 region was involved in various immune-mediated diseases, such as asthma, atopic dermatitis and BD (99, 100). Genetic ablation of IL18R1 or blockade of IL-18 receptor signaling could protect mice from autoimmune disease (98, 101).Three SNPs (rs12999364, rs12987977, and rs4851569) located in the IL1RL1–IL18R1 region were associated with ocular manifestations in Chinese BD patients. Among them, rs12987977 showed the strongest association with BD (P value=8.93e10−7, OR=0.39). Further investigations demonstrated that rs12987977/GG genotype resulted in decreased production of IFN-γ or TNF-α, indicating its anti-inflammatory role (49).

SINGLE NUCLEOTIDE POLYMORPHISMS IN MICRORNA

MicroRNA (MiRNA), a member of noncoding RNAs, functions in regulating gene expression by inducing cleavage, degradation, or block translation of messenger RNA. Over the last decade, multiple studies showed that miRNAs participate in the post-transcriptional gene regulation of BD and could be used as diagnostic biomarkers (102, 103). In an Iranian population, a significantly increased expression of miR-155 was observed in the PBMCs of BD patients as compared with controls (104). Jadideslam et al. confirmed that in BD patients from Iran the production of miR-21 and miR-146b decreased significantly, while the production of miR-326 increased significantly. MiR-326 expression level was proposed to be a biomarker to predict severe ocular involvement in BD patients (105). In addition, higher proportions of the G/G genotype and G allele of miR-146a rs2910164 variant were found in BD patients as compared with the healthy (55). Other altered expression of miR-25, miR-106b, miR-326 and miR-93, miR-182, miR-638, and miR-4488 has also been described in BD (106–109). However, the specific mechanism how the variants in MiRNA confer risk to BD remains unknown.

SINGLE NUCLEOTIDE POLYMORPHISMS IN OTHER GENES

The Janus kinase (JAK)/signal transducers and activators of transcription (STAT) pathway exerts important functions in multiple immune-mediated diseases. Many clinical trials made

progress in treating autoimmune diseases using JAK inhibitors, including rheumatoid arthritis (110), psoriatic arthritis (111), ulcerative colitis (112) and psoriasis (113). Several case reports also indicated that targeting JAK/STAT pathway could alleviate the progression of uveitis (114–116). Tofacitinib, a JAK1/3 inhibitor targeting T cell signaling, was shown to be effective for BD patients (117). Our previous study demonstrated that multiple SNPs of JAK1 contributed to the genetic susceptibility of BD with ocular involvement, including rs2780815, rs310241, rs3790532 (118). STAT4 belongs to the STAT family that regulate s gene transcription in response to type I interferon (IFN-I) and various cytokines of IL family (119). STAT4 has been implicated in T-helper cell differentiation, natural killer (NK) cell activation and IFNγ production and contributes to multiple inflammation and autoimmune diseases (119, 120). Recent studies have identified many susceptibility loci of STAT4 in a variety of diseases including rheumatoid arthritis (RA) (121, 122), systemic lupus erythematosus (SLE) (121, 122) and BD (13). A GWAS study initially reported susceptibility locus of rs7574070 STAT4 for BD in Turkish populations, which was replicated in Japanese, Chinese and Iranian populations (22, 27, 33). We found that SNPs rs7572482 and rs897200 in STAT4 were also shown to be associated with BD in a Han Chinese GWAS (22). Among them, the rs897200 risk genotype AA was associated with higher expression of STAT4 and severer clinical symptoms including. This GWAS in Han Chinese population totally identified 10 non-HLA SNPs which showed genome-wide significant associations with BD, including rs17006292 in TFCP2L1 for the first time (22).

TRAF5, a polymorphic gene, is a closely related member of tumor necrosis factor-receptor-associated factors (TRAF) family. It was identified to be associated with various autoimmune diseases including inflammatory bowel disease, diabetes and rheumatoid arthritis (31, 123). In, 2013, a case-control study in Han Chinese descent found that SNP rs12569232, rs10863888 and rs6540679 in TRAF5 conferred susceptibility to BD. Additionally, further investigations showed that TRAF5 gene polymorphisms contributed to regulating TRAF5 production as well as downstream inflammatory cytokines including TNF-α and IL-6 (31). Recently, some SNPs were shown to regulate the expression of long non-coding RNAs (lincRNAs) and then influence disease progression. The SNP rs12569232–residing in the non-coding site of the intergenic region between linc00467 and TRAF5 may affect the pathogenesis of BD through increasing the expression of linc00467. Moreover, the study suggested that overexpression of linc00467 enhanced cell viability of $CD4^+$T cells, which was essential to immune response in BD patients (124).

Recently, SNP rs9494885 in the tumor necrosis factor alpha-inducible protein 3 (TNFAIP3) was also identified to be genome-wide significantly associated with BD susceptibility in a Chinese Han population (26). However, no differences in TNFAIP3 expression was shown in different genotypes of rs9494885 (26). Therefore, SNP rs9494885 conferred risk to BD probably through an unknown mechanism rather than directly regulating TNFAIP3 expression.

With a high prevalence of BD in Turkey, studies have reported various novel susceptibility SNPs with genome-wide significance for BD in Turkey, including rs7616215 in CCR1, rs2230801, rs10094579 in RIPK2, rs224127, rs1509966 in ADO-ZNF365-EGR2, rs2617170 in KLRC4, rs2121033 in LACC1, rs61752717 in MEFV, rs7203487, rs142105922, rs11117433 in IRF8, rs681343 in FUT2, rs913678 in CEBPB-PTPN1 (27, 28, 44). Many of those were replicated by Iranian, Japanese and Han Chinese (33, 36, 47, 64).

To demonstrate genetic association between the CCR1/CCR3 gene and BD, we carried out a two-stage case control study in Chinese Han population. The combined studies showed that three SNPs (rs13092160, rs13084057, and rs13075270) conferred risk to BD. Among them, rs13092160 reached the GWAS significance threshold (P value<5e10−8) (24). Additionally, our recent GWAS study in Chinese BD confirmed 7 previously reported variants and proposed 22 novel susceptibility loci in the non-HLA region. The genome-wide significant associations of ZMIZ1, IL10RA, RPS6KA4, SIPA1-FIBP-FOSL1 and VAMP1 with BD were identified (52). Another Chinese candidate association study showed that rs9316059 in LACC1 has an association with BD at the genome-wide level of significance (47). Additionally, a Spanish study identified a novel genetic marker for BD, SNP rs2848479 in JRKL/CTCN5, with a genome-wide association (41).

Besides confirming six previously reported susceptibility variants in BD, a study of 9,444 patients and controls from seven different populations identified two novel genome-wide significant loci: rs4896243 in IFNGR1 and rs1660760 within the intergenic region of LNCAROD/DKK1 (54). Another variant in IFNGR1, rs9376268, was also shown to be involved in BD in the Chinese GWAS (52). IFNGR1 is the gene encoding the ligand-binding chain (alpha) of the interferon-gamma receptor, playing an essential role in cell immune response in BD (52). As a growing number of genetic variants have been identified with susceptibility to BD, various studies showed the correlation between genetic variants and specific manifestations of BD (**Table 3**).

COPY NUMBER VARIATIONS

Recently, an increasing number of studies showed that the main cause of structural variation in the genome is copy number variation (CNV). It represents large fragments of DNA sequence variation, involving insertions, duplications, and deletions of sequences (8, 137). CNV significantly contributes to human genetic diversity by influencing the gene expression. Therefore such variations have been found to be associated with autoimmune disorders including BD (56), SLE (138), RA (139) and Grave's disease (140).

Since complement activation is involved in various immune-mediated diseases, the association of CNV in complements with BD is worthy to study. A previous study detected the copy number of C4 in 905 patients with BD, 205 patients with ankylosing spondylitis (AS) and acute anterior uveitis (AAU), and 1,238 controls by real-time PCR test. A significantly higher ratio of more than 2 copies of C4A patients were observed in BD.

TABLE 3 | The correlation between genetic variants and specific manifestations of BD.

Gene	SNP	Risk Allele/Genotype	Manifestation	Population	PMID
IL-23R	rs7517847	G	genital ulcers	Turkish population	(125)
	rs11805303	G	papulopustular lesions		
	rs1004819	G	papulopustular lesions		
MVK	rs35191208	C	neurological involvements	Turkish population	(126)
ERAP1	rs30187	TT	cardiac involvements	Iranian population	(127)
	rs30187	TT	articular involvements	Iranian HLA-B*51 positive population	
IL-27	rs153109	AG/GG	joint and vascular involvements	Iranian population	(128)
CD40	rs4810485	GT	skin lesions	Turkish population	(129)
CD40	rs1883832	CC	genital ulcers		
IL-10	rs1800896	A	genital ulcer	Egyptian population	(130)
		G	ocular manifestations		
IL17A	rs8193036	TT	intestinal involvements	Korean population	(131)
IL23R	rs1884444	GG/GT	intestinal involvements		
CTLA-4	rs231775	A	ocular and vasculitic manifestations	Egyptian population	(132)
JAK1	rs2780815	G	ocular involvements	Chinese Han population	(118)
	rs310241	C	ocular involvements		
	rs3790532	A	ocular involvements		
PTPN2	rs1893217	C	gastrointestinal involvements	Chinese Han population	(133)
	rs2542151	GT	gastrointestinal involvements		
MIF	rs755622	C	oral aphthae, genital ulceration, hypopyon, and arthritis involvements	Chinese Han population	(134)
	rs2096525	C	oral aphthae, genital ulceration, hypopyon, and skin lesion		
IL-10	rs1800871	T	genital ulcers, skin lesions	Chinese Han population	(135)
ERAP1	rs17482078	GA	neurological involvements	Italian population	(136)
IL23R	rs17375018	GG	neurological involvements		

However, there was no significance in AS and AAU patients. Functional studies suggested that the high copy number of C4a could moderate C4a expression and promote IL-6 production, which was regarded as a risk factor for BD (56). Additionally, BD patients showed a remarkable high frequency of covering over two copies of C3 and C5 (58).

Toll-like receptors (TLRs), members of pattern-recognition receptors (PRRs), were indicated to be associated with the pathogenesis of various inflammatory or autoimmune human diseases (141, 142). In a Chinese Han population, a research unprecedent declared that the risk of BD could be increased by high copies of the TLR7 gene. TLR7 is located on the X chromosome. The frequencies of >1 copy of TLR7 in male BD patients and >2 copies in female patients were increased, suggested the difference between genders (57).

As a growing number of studies discovered apoptosis-related genes playing critical roles in various autoimmune diseases, recent research investigated whether the CNVs of these genes were associated with BD (61, 143–145). The high copy number of FAS gene, one of the apoptosis-related genes, was identified to be strongly associated with BD (61).In addition, frequencies of more than 2 copies of IL17F and IL23A were significantly increased in Chinese male BD patients as compared with controls (59). Other CNVs associated with BD include Rorc and Foxp3 gene variants (60).

EPIGENETIC MODIFICATIONS

Epigenetics usually refer to the heritable changes in gene expression without the DNA sequences alterations (102). It contributes to control gene expression and modulate cell development, differentiation, and activity (146). Epigenetic modifications, containing DNA methylation and histone modification, are considered to be associated with the pathogenesis of BD (62).

DNA methylation is universally considered as the main epigenetic modification of autoimmune diseases. DNA methylation is the covalent addition of methyl groups to the fifth carbon (C5) in the cytosine base, which may regulate physiological and pathological processes (102). A study found a high expression level of IL-6 gene in BD patients with decreased promoter methylation level of the IL-6 mRNA. The change in the methylation level of the IL-6 may be associated with susceptibility to BD (147). Additionally, expression level of the IL-10 gene decreased in BD patients with a high promoter methylation level. Interestingly, the high IL-10 methylation level is significantly associated with severe symptoms in BD patients (148).

An epigenome-wide association study (EWAS) showed, 4332 BD-related differentially methylated CpG sites in Han Chinese. Among them, five methylated sites (cg03546163, cg25114611, cg20228731, cg23261343, and cg14290576) in four genes (FKBP5, FLJ43663, RUNX2, and NFIL3) were significantly hypomethylated. Especially, the study discovered significant overexpression of FKBP5 mRNA with the hypomethylation at cg03546163 and cg25114611 in FKBP5 (149).

Histone modifications, including acetylation, methylation, SUMOylation, and ubiquitination, could influence the chromatin structure and gene expression (62). Sirtuin 1 (Sirt1), a histone deacetylase, which could inhibit NF-κB transcription and T-cell proliferation, promote TNF-α induced apoptosis and affect immune tolerance through regulating histone acetylation, was considered as a risk factor for BD with uveitis (150). However, future studies are needed for the full comprehension how epigenetic modifications confer susceptibility to BD.

CONCLUSION

Uveitis is a sight-threatening inflammatory ocular disease, among which BD is one of the most common and complex entities. Although the pathogenesis of BD is not entirely understood, specific HLA types and gene variants in non-HLA regions have been identified to contribute to the susceptibility of BD. Specifically, SNPs as well as CNVs play critical roles in the gene variants. In addition, epigenetic modifications including DNA methylation and histone modification were also implicated in the development of BD. However, the identified gene variants still account for a small part of the pathogenesis of BD. A large number of BD-related gene variants have yet to be explored.

AUTHOR CONTRIBUTIONS

YG, ZZ, and PY conceived the structure of manuscript. YG drafted initial manuscript. YG and ZZ made the tables. PY and ZZ revised this manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

The work was supported by the Chongqing Key Laboratory of Ophthalmology (CSTC, 2008CA5003), Chongqing Outstanding Scientists Project (2019), Chongqing Chief Medical Scientist Project (2018), Chongqing Science & Technology Platform and Base Construction Program (cstc2014pt-sy10002).

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