



Antineutrophil Cytoplasmic Antibody-Associated Vasculitis Update: Genetic Pathogenesis

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Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is characterized by the inflammation of small and medium vessels and presence of proteinase 3-ANCA or myeloperoxidase-ANCA in the circulation. AAV comprises three clinical subtypes: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic GPA (EGPA). Although the pathogenesis of AAV is still unclear, genetic and environmental factors and the immune system are thought to be involved. Genetic factors have been confirmed to play an important role in AAV. Genome-wide association studies have identified numerous genetic variants in MHC and non-MHC regions associated with AAV. The strongest evidence of MHC association in AAV is human leukocyte antigen (HLA)-DP. A significant association between AAV and genetic variations in non-MHC regions, such as *CTLA-4*, *FCGR2A*, *PTPN22*, *SERPINA1*, and *TLR9* has also been found. Moreover, different clinical subtypes of AAV have distinct genetic backgrounds. GPA is associated with *HLA-DP1*, MPA with *HLA-DQ*, and EGPA with *HLA-DRB4*. These findings could help elucidate the etiology of AAV and develop new biomarkers for diagnosis and targeted therapy. Herein, we briefly summarize the updates on the genetic pathogenesis and biomarkers of AAV.

Keywords: vasculitis, antineutrophil cytoplasmic antibody, genetic, genome-wide association studies, variation

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a complex systemic autoimmune disease presenting with the inflammation of small and medium vessels that results in vascular destruction and tissue necrosis (1, 2). AAV is divided into three groups according to clinical features: granulomatosis with polyangiitis (GPA, formerly called Wegener's granulomatosis), microscopic polyangiitis (MPA), and eosinophilic GPA (EGPA, formerly called Churg-Strauss syndrome) (3). The disease is characterized by the presence of proteinase 3 (PR3)-ANCA or myeloperoxidase (MPO)-ANCA in the serum. GPA is predominantly associated with PR3-ANCA,

while MPA and EGPA are predominantly associated with MPO-ANCA, but are also occasionally ANCA-negative (4). EGPA is often divided into two subtypes, MPO-ANCA+ EGPA and ANCA- EGPA. Vasculitis can occur in any organ or tissue, commonly affecting the respiratory tract and kidneys, causing life-threatening kidney failure or pulmonary hemorrhage (3).

AAV has an estimated prevalence of 48–184/1,000,000 individuals worldwide, while the incidence and prevalence in Europe are higher than those in other regions (2). The annual incidence in Europe is 4.9–10.6/1,000,000 individuals for GPA, 2.7–11.6/1,000,000 individuals for MPA, and 0.5–3.1/1,000,000 individuals for EGPA. The epidemiological manifestations of AAV differ among geographical regions; GPA and PR3-ANCA AAV are more common in Europeans, while MPA and MPO-ANCA AAV are more common in Asians (5).

Although the pathogenesis of AAV remains elusive, it is believed that both genetic and environmental components are involved. Environmental factors, including silica exposure, bacterial or viral infections, and drugs suggest an association with the occurrence and relapse of AAV (6). Familial studies and genetic association studies have demonstrated that AAV has a background of genetic susceptibility (7–9). It has been estimated that 20% of AAV risk is due to genetic factors (10).

In this review, we mainly discuss the genetic studies on AAV, focusing on the identified susceptibility genes or loci to enrich our understanding of the disease.

GENETIC APPROACHES FOR AAV

Different genetic approaches have revealed that a large number of genes are related to AAV. First, several candidate gene association studies have been used to identify susceptibility genes associated with AAV. Although these approaches are easy to carry out, they are prone to false-positive results. Human leukocyte antigen (*HLA*), *PTPN22*, *CTLA-4*, *IL-10*, and *TLR9* have been found to be associated with AAV (11, 12). The emergence of genome-wide association studies (GWAS) has led to their wide use in exploring the genetic factors involved in various diseases. GWAS is a powerful approach to identify the genetic architecture of complex diseases, and it has made major contributions towards a better understanding of AAV genetics. Four GWAS have been performed in patients with AAV since 2012 (two for MPO and GPA (13, 14), one for GPA (15), and one for EGPA (16)). The latest GWAS was on EGPA in 676 cases and 6809 controls with the identification of 11 loci associated with EGPA. The study also revealed that EGPA comprises genetically distinct subgroups, that MPO-ANCA+ subgroup was strongly associated with HLA-DQ and MPO-ANCA- subgroup was associated with non-HLA regions, such as GPA33 and *IL5/IRF1* (16). All these GWAS studies were conducted in populations with European ancestry and have identified more than 20 genes associated with AAV. The findings of GWAS are listed in **Tables 1** and **2**. In addition, meta-analysis and fine mapping have also been used to identify new gene variations and analyze the effect of the variants (17–21).

AAV SUSCEPTIBILITY GENES

HLA Region

HLA

HLA, located on chromosome 6p21, is the most gene-dense region of the human genome and contains diverse genes involved in key immune responses (22). Molecules encoded by *HLA* participate in a variety of immune and inflammatory pathways. *HLA* single-nucleotide polymorphisms (SNPs) are associated with numerous human diseases, especially autoimmune diseases, such as type 1 diabetes, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) (23). Since AAV is considered an autoimmune disease, *HLA* may also be a potential predisposing factor for AAV. Candidate gene studies in *HLA* regions were performed in different populations, including the Swedish, Germans, and Italians in Europe and Japanese and Chinese in Asia. *HLA-DPA1*, *HLA-DPB1*, *HLA-DQA1*, *HLA-DQB1*, and *HLA-DRB1* were found to be involved in AAV susceptibility.

(1). HLA and AAV

Two GWAS were performed to identify the genetic factors associated with AAV. The first GWAS in a European population in 2012 demonstrated that *HLA-DP* rs3117242 (G) was the strongest signal in the HLA region ($P = 1.5 \times 10^{-71}$, OR = 3.67) (13). Another GWAS in Canadian and American populations conducted in 2017 showed that SNPs rs141530233 and rs1042169 at *HLA-DPB1* had the largest effect on the risk of developing AAV ($P = 1.13 \times 10^{-89}$, OR = 2.99; $P = 1.12 \times 10^{-84}$, OR = 2.82, respectively). *HLA-DPA1*, *HLA-DQA1*, and *HLA-DQB1* are also risk alleles that may cause AAV (14). These studies not only indicated a highly significant association between AAV and *HLA* regions but also showed genetic distinctions between different clinical phenotypes and ANCA specificity. GPA and PR3-ANCA AAV are associated with *HLA-DPB1* and *HLA-DPA1*, while MPA and MPO-ANCA AAV are associated with *HLA-DQB1* and *HLA-DQA2*.

(2). HLA and GPA

GWAS for GPA with 492 patients and 1,506 healthy individuals of European descent identified 32 SNPs across the HLA region; among them, *HLA-DPB1* rs9277554 and *HLA-DPA1* rs9277341 were significantly associated with GPA in the combined cohort (15). In another study with 150 GPA patients and 100 healthy controls conducted in northern Germany, *HLA-DPB1**0401 was identified to be associated with GPA ($P = 1.51 \times 10^{-10}$, OR = 3.91), and *DPB1**0401/*RXR*B03 haplotype frequency was significantly increased in patients with GPA ($P = 7.13 \times 10^{-17}$, OR = 6.41) (18). The result was replicated in an independent German cohort with 108 patients with GPA ($P = 6.4 \times 10^{-8}$) (20). *HLA-DPB1* was also considered a genetic risk factor for GPA in a cohort of 176 Han Chinese patients with AAV (100 with GPA, 76 with MPA) and 485 healthy controls ($P = 1.83 \times 10^{-5}$, OR = 2.57). In this study, the result also showed that the *HLA-DPB1* SNP rs3117242 variant T allele was significantly associated with GPA patients ($P = 6.24 \times 10^{-5}$, OR = 2.09), but not with MPA patients (24).

TABLE 1 | A summary of main genetic associations with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis through genome-wide association studies, according to Clinical subgroups.

Subgroups	Chr	Reported Gene(s)	SNP	Population	Cases-Controls	P-value	OR	Reference (PMID)	
GPA and MPA	1p13.2	<i>PTPN22</i>	rs2476601	European	1986-4723	1.86×10^{-7}	1.36	28029757	
	1p13.2	<i>PTPN22</i>	rs6679677	European	1986-4723	1.88×10^{-8}	1.4	28029757	
	6p21.32	<i>HLA-DP</i>	rs3117242	European	2267-6858	1.5×10^{-71}	3.67	22808956	
	6p21.32	<i>COL11A2</i>	rs3130233	European	2267-6858	7.8×10^{-15}	1.51	22808956	
	6p21.32	<i>COL11A2</i>	rs3117016	European	2267-6858	6.4×10^{-24}	1.83	22808956	
	6p21.32	<i>SERPINA1</i>	rs7151526	European	2267-6858	2.4×10^{-9}	0.59	22808956	
	19p13.3	<i>PRTN3</i>	rs62132295	European	1353-1599	7.1×10^{-5}	0.78	22808956	
	6p21.32	<i>HLA-DPB1</i>	rs141530233	European	1986-4723	1.13×10^{-89}	2.99	28029757	
	6p21.32	<i>HLA-DPB1</i>	rs1042169	European	1986-4723	1.12×10^{-84}	2.82	28029757	
	6p21.32	<i>HLA-DPA1</i>	rs9277341	European	1986-4723	6.09×10^{-71}	2.44	28029757	
	6p21.32	<i>HLA-DQA1</i>	rs35242582	European	1986-4723	6.34×10^{-23}	1.6	28029757	
	6p21.32	<i>HLA-DQB1</i>	rs1049072	European	1986-4723	6.46×10^{-13}	1.4	28029757	
	6p21.32	<i>SERPINA1</i>	rs28929474	European	1986-4723	3.09×10^{-12}	2.18	28029757	
	19p13.3	<i>PRTN3</i>	rs62132293	European	1986-4723	8.60×10^{-11}	1.29	28029757	
	GPA	5q23.1	<i>SEMA6A</i>	rs26595	European	987-2731	2.9×10^{-8}	0.74	23740775
		6p21.3	<i>HLA-DPA1</i>	rs9277341	European	750-1820	2.18×10^{-39}	0.33	23740775
		6p21.3	<i>HLA-DPB1</i>	rs9277554	European	750-1820	1.92×10^{-50}	0.24	23740775
		6p21.32	<i>HLA-DP</i>	rs3117242 (G)	European	1683-6858	3.1×10^{-85}	5.39	22808956
		6p21.32	<i>HLA-DPB1</i>	rs141530233	European	1556-4723	3.8×10^{-93}	3.82	28029757
6p21.32		<i>HLA-DPB1</i>	rs1042169	European	1556-4723	1.09×10^{-90}	3.66	28029757	
6p21.32		<i>HLA-DPA1</i>	rs9277341	European	1556-4723	2.78×10^{-73}	2.86	28029757	
6p21.32		<i>HLA-DQA1</i>	rs35242582	European	1556-4723	1.6×10^{-20}	1.63	28029757	
6p21.32		<i>SERPINA1</i>	rs7151526	European	1683-6858	4.4×10^{-10}	0.54	22808956	
6p21.32		<i>SERPINA1</i>	rs28929474	European	1556-4723	3.53×10^{-13}	2.35	28029757	
19p13.3		<i>PRTN3</i>	rs62132293	European	1556-4723	7.06×10^{-11}	1.32	28029757	
Xp22.2		<i>MOSPD2</i>	rs6628825	European	1683-6858	2.6×10^{-5}	0.8	22808956	
MPA		6p21.32	<i>HLA-DQB1</i>	rs1049072	European	236-4723	4.16×10^{-9}	1.89	28029757
	EGPA	2q13	<i>BCL2L11</i>	rs72946301	European	534-6809	9.0×10^{-11}	1.81	31719529
5q22.1		<i>TSLP</i>	rs1837253	European	534-6809	5.2×10^{-11}	1.52	31719529	
6p21.32		<i>HLA-DQ</i>	rs9274704	European	534-6809	1.2×10^{-20}	2.01	31719529	
	10p14	<i>10p14</i>	rs34574566	European	534-6809	2.9×10^{-8}	0.7	31719529	

TABLE 2 | Summary of main genetic associations with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis through genome-wide association studies, according to ANCA subgroups.

Subgroups	Chr	Reported Gene(s)	SNP	Population	Cases-Controls	P-value	OR	Reference	
PR3+ AAV	6p21.32	<i>HLA-DP</i>	rs3117242	European	1521-6858	6.2×10^{-89}	7.03	22808956	
	6p21.32	<i>HLA-DPB1</i>	rs141530233	European	1361-4723	1.33×10^{-106}	6.19	28029757	
	6p21.32	<i>HLA-DPB1</i>	rs1042169	European	1361-4723	6.53×10^{-106}	6.09	28029757	
	6p21.32	<i>HLA-DPA1</i>	rs9277341	European	1361-4723	4.52×10^{-84}	3.69	28029757	
	6p21.32	<i>HLA-DQA1</i>	rs35242582	European	1361-4723	5.78×10^{-18}	1.62	28029757	
	6p21.32	<i>SERPINA1</i>	rs28929474	European	1361-4723	1.29×10^{-13}	2.43	28029757	
	19p13.3	<i>PRTN3</i>	rs62132295(A)	European	1521-1599	2.6×10^{-7}	0.73	22808956	
	19p13.3	<i>PRTN3</i>	rs62132293	European	1361-4723	3.59×10^{-13}	1.39	28029757	
	6q22.33	<i>ARHGAP18</i>	rs1705767	European	1521-6858	5.2×10^{-8}	0.73	22808956	
	14q32.13	<i>SERPINA1</i>	rs7151526	European	1521-6858	5.6×10^{-12}	0.53	22808956	
	Xp22.2	<i>MOSPD2</i>	rs6628825	European	1521-6858	6.1×10^{-7}	0.77	22808956	
	MPO+ AAV	6p21.32	<i>HLA-DQ</i>	rs5000634	European	556-6858	2.1×10^{-8}	0.65	22808956
		6p21.32	<i>HLA-DQA2</i>	rs3998159	European	378-4723	5.24×10^{-25}	2.72	28029757
6p21.32		<i>HLA-DQA2</i>	rs7454108	European	378-4723	5.03×10^{-25}	2.73	28029757	
MPO- AAV	6p21.32	<i>HLA-DQB1</i>	rs1049072	European	378-4723	2.13×10^{-24}	2.37	28029757	

(3). HLA and MPA

There was no specific GWAS study for MPA, but the clinical subgroup analysis of AAV GWAS demonstrated that *HLA-DQB1* was significantly associated with MPA ($P = 4.16 \times 10^{-9}$, OR = 1.89) (14). A significant association of *HLA-DRB1*0901* with MPA ($P = 0.0037$, OR = 2.44) and MPO-AAV ($P = 0.0014$, OR = 2.44) was demonstrated in 50 MPA and 64 MPO-ANCA AAV cases compared with 265 controls in a Japanese cohort (25). The result was confirmed with new

observations that *DRB1*13:02* was associated with protection against MPA and MPO-ANCA AAV in 468 Japanese patients with AAV and 596 controls ($P = 2.1 \times 10^{-4}$, OR = 1.57) (26). In a small cohort of 50 patients with MPA and 77 Japanese controls, *DQB1*0303* was significantly associated with MPA ($P = 0.017$, OR = 2.35) (27). A recent study genotyped *HLA-DRB1*, *DQA1*, *DQB1*, *DPB1*, and *HLA-DP* in 258 patients with MPO-AAV and 597 healthy controls in the Chinese population and found that *HLA-DQA1*0302* ($P = 3.45 \times 10^{-9}$,

OR = 2.34) and *DQB1*0303* ($P = 3.26 \times 10^{-9}$, OR = 1.89) were risk alleles for MPO-ANCA AAV (28).

(4). HLA and EGPA

A recent GWAS for EGPA including 676 EGPA cases and 6,809 controls in European populations showed that *HLA-DQ* was strongly associated with EGPA at genome-wide significance ($P = 1.2 \times 10^{-20}$, OR = 2.01), especially MPO-ANCA EGPA ($P = 1.1 \times 10^{-28}$, OR = 5.68) (16). This result was consistent with a study comprising 102 German patients with EGPA ($P = 2.00 \times 10^{-5}$, OR = 1.87) (29) as well as another study with 48 Italian patients ($P = 2.32 \times 10^{-4}$, OR = 2.49) (30). The Italian study also revealed that *HLA-DRB1*07* allele frequency was significantly higher in patients with EGPA than in controls ($P = 0.42 \times 10^{-2}$, OR = 2.42) (30).

Furthermore, *HLA* alleles were associated with the severity, prognosis, and relapse of AAV. *HLA-DRB1*04:05* was associated with poor renal prognosis; *HLA-DRB1*04:02* was associated with high mortality (31); and *DPB1*04:01* was significantly associated with an increased risk of relapse (32).

AAV is an autoimmune disease. The identification of *HLA*-alleles associated with AAV confirm the centrality of auto-reactivity in the development of AAV, help us make a better understanding about its autoimmune pathogenesis, and point to logical therapeutic strategies. The identification of *HLA*-alleles not only can help us to distinguish from cases of GPA, MPA and EGPA and their subtypes, but also to evaluate and predict the severity, prognosis, and relapse of AAV.

Retinoid X Receptor Beta

RXRβ, located on 6p21.32, encodes a member of the retinoid X receptor family of nuclear receptors. Strong associations of *RXRβ* with GPA were revealed through the markers located in the *HLA* region and *RXRβ* loci. Because *RXRβ* located in the *HLA* region near *HLA-DPB1*, *HLA-DPB1*0401/RXRβ03* haplotype was found to be strongly associated with GPA ($P = 7.13 \times 10^{-17}$, OR = 6.41) (18). *RXRβ* SNP rs6531 ($P = 5.20 \times 10^{-5}$, OR = 1.88) was significantly increased among patients with GPA compared to controls (19). The result was confirmed in a later meta-analysis, which included 140 genetic variants associated with AAV (17).

Ring Finger Protein 1

RING is also located in the *HLA* region, near *HLA-DPB1*. *RING* is a member of the polycomb repressive complex 1 that mediates histone H2A polyubiquitination and monoubiquitination, regulating its gene expression. Three SNPs in the region near *RING1* (rs213210, rs213209, and rs213208) were found to be associated with GPA in German patients (20). The *HLA-DPB1/RING1* haplotype is strongly associated with GPA in ANCA-positive subjects.

Non-*HLA* Region

Genes Encoding ANCA Associated Proteins

Serpin family A Member 1

SERPINA1, located on 14q32.13, encodes α 1-antitrypsin, which is the major inhibitor of PR3 and is thought to limit the damage

to local tissues (33). In AAV, the genetic variants of *SERPINA1* may lead to the decreased function of α 1-antitrypsin, potentially resulting in ANCA generation as PR3 accumulates in tissues, causing the inflammation of blood vessels. The first AAV GWAS reported that the *SERPINA1* Z allele along with the rs7151526 risk allele were significantly associated with AAV and were the most prominent non-*HLA* regions associated with both PR3-ANCA and GPA subgroups (13). Another GWAS confirmed the result with the identification of *SERPINA1* rs28929474, which was associated with AAV ($P = 3.09 \times 10^{-12}$, OR = 2.18), especially associated with GPA ($P = 3.53 \times 10^{-13}$, OR = 2.35) (14). Several studies have investigated the role of the Z allele in AAV and showed that heterozygous patients for the Z variant of *SERPINA1* have an increased risk of developing GPA than the general population (34, 35).

Proteinase 3 (PRTN3)

PRTN3, located on 19p13.3, encodes PR3. PR3 is a neutrophil intracellular protease that is the main antigen of ANCA autoantibodies. PR3 is located on the plasma membrane of a subset of neutrophils and stored in the neutrophil azurophilic granules. The membrane-bound form interacts directly with ANCA (33), decreasing neutrophil activation and endothelial adhesion.

In a Swedish cohort of 79 patients with GPA and 129 controls, the coding and promoter sequences of *PRTN3* were investigated. An association with GPA was demonstrated by *PRTN3* A564G variation in the promoter region affecting a transcription factor-binding site ($P < 0.00001$, OR = 4.2) (36). The association of *PRTN3* has been reported in two GWAS of AAV. Subgroup analysis revealed that *PRTN3* SNP rs62132295 and rs62132293 were significantly associated with AAV, especially PR3-AAV or GPA ($P = 2.6 \times 10^{-5}$, OR = 0.78; $P = 8.60 \times 10^{-11}$, OR = 1.29) (13, 14). As observed for the above-mentioned *HLA* association, the strength of the *PRTN3* SNP signal increased in the PR3-ANCA-positive subgroup, independent of the clinical diagnosis ($P = 2.6 \times 10^{-7}$, OR = 0.73). No association between *PRTN3* and patients with MPA or MPO-AAV was found, which indicates that *PRTN3* only plays a crucial role in the pathogenesis of anti-PR3-positive AAV.

Immunoregulatory Genes for AAV

Protein Tyrosine Phosphatase, Non-Receptor Type 22

PTPN22, located on 1p13.2, encodes lymphoid tyrosine phosphatase (Lyp), a member of the non-receptor class 4 subfamily of the protein tyrosine phosphatase family. *PTPN22* 620W variation causes the substitution of arginine with tryptophan at amino acid residue 620, disturbing the function of *PTPN22*, which is involved in B-cell receptor and T cell receptor signaling, causing autoimmune diseases. It is associated with type 1 diabetes, RA, SLE, and other autoimmune disorders (37, 38).

The 620W allele conferred susceptibility to AAV in a German cohort ($P = 0.002$, OR = 1.75), and the allele frequency was significantly increased in ANCA-positive GPA ($P < 0.0002$) (39). This result has been confirmed in a British cohort ($P = 1.4 \times 10^{-4}$, OR = 1.40) (40) and an Italian cohort ($P = 0.005$, OR = 1.91)

(41). A meta-analysis of four studies in 1,399 patients of European descent found the association between the *PTPN22* 620W allele and the occurrence and development of AAV (42).

Cytotoxic T Lymphocyte-Associated Antigen-4

CTLA4, located on 2q33.2, encodes an inhibitory glycoprotein expressed on activated T cells, which transmits an inhibitory signal to T cells. *CTLA4* competes with CD28 to bind to CD80 and CD86, which function antagonistically. *CTLA4* is a negative regulator of T cell activation and inhibits the immune response, while CD28 transmits a stimulatory signal. The expression of *CTLA4* on CD4 T cells is increased in GPA (43). Mutations on this gene have been associated with Graves' disease, celiac disease, SLE, and other autoimmune diseases.

Although the *CTLA4* SNP did not show genome-wide association in the GWAS of AAV, the association with AAV was found in candidate gene studies in different populations. *CTLA4* rs3087243 showed an association with AAV in 641 British AAV cases and 9,115 controls ($P = 6.4 \times 10^{-3}$, OR=0.84). *CTLA4* exon 1 (+49) and 4 (CT60) polymorphisms showed an association with AAV in another independent British cohorts with 222 cases and 629 controls ($P_{(+49)} = 0.004$, $P_{(CT60)} = 0.002$, respectively) (40, 44). The similar result was confirmed in a Swedish cohort with 101 cases and 200 controls ($P = 0.049$) (45).

Toll-Like Receptors

TLRs, located on chromosome 3p21.2, encode a family of innate receptors whose specificities are predetermined in the germline. *TLRs* can recognize microbiological structures and activate immune responses that participate in the development of autoimmune diseases (46). Infection, particularly *Staphylococcus aureus* infection, is considered a potential trigger of AAV, and *TLR9* signaling may be involved in disease pathology, favoring models of infectious agents triggering AAV development (47). SNPs in *TLR9* were genotyped in a German cohort comprising 863 patients with AAV and 1,344 healthy controls to investigate the contribution of genetic polymorphisms of *TLR9* to the susceptibility and clinical manifestation. Strong association of *TLR9* genotypes and haplotypes with the subgroups of GPA and MPA was observed, but no association was observed with EGPA. In a cohort of 426 Dutch and British AAV cases, the findings were not replicated (21). *TLR9* signaling may be involved in disease pathology, favoring models of infectious agents triggering AAV development.

Fc Gamma Receptors

FCGRs are a group of proteins expressed on the surface of different cell types with different affinities for the Fc portions of different IgG subclasses. The key role of Fc receptors is the regulation of inflammatory and immune responses. *FCGR3B* encodes FcγRIIIB, which is expressed by neutrophils and eosinophils and is important in the tethering of neutrophils to immune complexes and the clearance of immune complexes (48). The *FCGR3B* copy number may play a role in the development of SLE or other autoimmune diseases (49).

In a study consisted with two independent cohorts of individuals with GPA from Britain and France, strong association between *FCGR3B* copy numbers and risk of GPA was shown. In British patients, low *FCGR3B* copy number was

found to be associated with GPA ($P = 0.015$, OR = 2.46), but in French GPA patients, the association with high *FCGR3B* copy number was identified ($P = 0.002$, OR = 0.28) (50). The study also explored the relationship between *FCGR3B* and MPA in a separate British cohort and observed a significant association between low *FCGR3B* copy number and MPA ($P = 0.013$, OR = 2.56). Later, the results were replicated in a large Chinese cohort with 139 AAV patients and 564 controls ($P = 0.040$, OR = 1.72) with the result that low *FCGR3A* CNVs were significantly associated with AAV susceptibility ($P = 0.042$, OR = 2.64) (51).

Possible associations of SNPs of *FCGR2A*, *FCGR2B*, *FCGR3A* and the *FCGR3B* haplotype NA1/NA2 and EGPA have been discussed in a recent study, which included 130 EGPA patients and 181 controls. *FCGR3B* haplotype NA1/NA2 was found to be associated with relapse-free survival of EGPA that relapse-free survival was significantly lower in carriers of *FCGR3B* haplotype NA1-NA1 than the others ($P = 0.029$). MPO-ANCA+ EGPA subgroup was also associated with relapse ($P = 0.032$) while no association was observed in MPO-ANCA- EGPA subgroup ($P = 0.68$) (52).

Interleukin-10

IL-10 is an anti-inflammatory cytokine produced by T helper cells, and its expression increases in patients with AAV (53). Two small studies in German and Caucasian cohorts proposed an association of *IL-10* SNP (-1082) in GPA (54); interestingly, one study also demonstrated a signal for the *IL-10* SNP in 36 patients with MPA ($P < 1.00 \times 10^{-6}$) (55). In a large German cohort of 403 patients with GPA, 103 patients with EGPA and 507 controls, none of the *IL-10* polymorphisms were associated with GPA, but *IL-10* -3575/-1082/-592 TAC haplotype was highly significantly associated with ANCA-negative EGPA ($P = 3.00 \times 10^{-5}$, OR = 2.16) (56).

Interleukin 2 Receptor Subunit Alpha

IL2RA encodes the high-affinity *IL-2* receptor, which is represented not only on the surface of T cells, but also on activated B cells, NK cells, and monocytes (57). The *IL2-IL2RA* pathway is critical for the physiological function of the immune system; survival, proliferation, and activation of T cells and development of a normal Treg repertoire (58). An association has been reported in a UK cohort of 670 patients with AAV for the *IL2RA* SNP rs41295061 ($P = 1.22 \times 10^{-2}$) (59), but no correlation between *IL2RA* and AAV was found during the replication stage of the first GWAS validation.

Other Susceptible Genes

Defensin Beta 4A

DEFB4 is an antibiotic peptide. The copy number variation of *DEFB4* reportedly causes susceptibility to inflammatory disorders (60). Higher *DEFB4* copy number was demonstrated to be significantly higher in a small cohort of 112 Chinese patients with AAV than in controls, which supported the role of the defensin system in autoimmunity (61).

Rho GTPase-Activating Protein 18

ARHGAP18 belongs to a family of Rho GTPase-activating proteins that modulate cell signaling. The subgroup analysis of

the first GWAS for AAV revealed that *ARHGAP18* was associated with GPA ($P = 3.3 \times 10^{-7}$, OR = 0.84) and PR3-ANCA AAV ($P = 5.2 \times 10^{-8}$, OR = 0.87) (13).

BCL2-Like11 and MIR4435-2HG(MORRBID)

BCL2L11 encodes BIM, which belongs to the BCL-2 protein family and is crucial for controlling apoptosis, immune homeostasis, and autoimmune diseases (62, 63). *MORRBID* encodes a long non-coding RNA that regulates BIM transcription, controls eosinophil apoptosis, and is dysregulated in hypereosinophilic syndrome (64). In the GWAS of EGPA, SNPs near *BCL2L11* and *MORRBID* were identified to be associated with EGPA ($P = 9 \times 10^{-11}$, OR = 1.66) (16).

Thymic Stromal Lymphopoietin

TSLP is located on 5q22.1. Its product, TSLP, is released by stromal and epithelial cells in response to inflammatory stimuli, which drives eosinophilia and enhances TH2 responses that are associated with immunity in various inflammatory diseases, including asthma, allergic inflammation, and chronic obstructive pulmonary disease (65). *TSLP* SNP rs1837253 which lies immediately upstream of *TSLP* was observed to be EGPA susceptibility variant ($P = 5.2 \times 10^{-11}$, OR = 1.42) (16).

ETS Proto-Oncogene 1

ETS1, located on chromosome 11q24.3, encodes a member of the ETS family of transcription factors. *ETS1* inhibits the differentiation of Th17 cells and induces the development of Tregs. Genetic variation may cause an increase in Th17 in patients with GPA, causing inflammation of small vessels. A GWAS in a Chinese population reported that *ETS1* SNP rs1128334 was significantly associated with SLE (66). In order to observe whether this gene was associated with other autoimmune diseases, a Japanese study which contained 466 patients with AAV and 1099 healthy controls was carried out. *ETS1* SNP rs1128334 was genotyped and found to be associated with GPA ($P = 0.030$, OR = 1.54) and PR3-ANCA AAV ($P = 0.021$, OR = 1.72) (67).

Telomerase Reverse Transcriptase and Desmoplakin

TERT is the catalytic subunit of telomerase and contributes to the maintenance of telomere length (68). *TERT* rs2736100A is associated with shorter leukocyte telomere length (69). *TERT* also has an anti-apoptotic effect, and a decreased expression of *TERT* associated with the risk allele may result in the enhancement of apoptosis (70). With the evidence that a proportion of T cells show short telomeres in patients with GPA and an enhancement in neutrophil apoptosis in patients with AAV, *TERT* has been proposed as a susceptibility gene for AAV (71). In a Japanese cohort comprising 544 patients with AAV and 5558 controls, the frequency of *TERT* rs2736100A alleles was significantly increased in MPA ($P = 2.3 \times 10^{-2}$, OR = 1.38) and MPO-AAV ($P = 0.15 \times 10^{-2}$, OR = 1.33) (72). *DSP* rs2076295G showed similar results to *TERT* rs2736100A ($P = 0.69 \times 10^{-2}$, OR = 1.32) in MPO-AAV ($P = 0.011$, OR = 1.26) (72). *DSP* reportedly modulates Wnt/ β -catenin signaling, which is involved in cell proliferation, differentiation, immune response, and carcinogenesis. Wnt signaling plays a role in autoimmune diseases and may also be associated with the onset of AAV.

TABLE 3 | Summary of genetic associations with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis excluding those derived from genome-wide association studies.

Gene	Variation	Disease	Populations
<i>HLA</i>	DQA1*0302, DQB1*0303, DPB1*04:01, DRB1*0901, DRB1*1101, DRB1*13:02, HLA-DPA1, HLA-DQA2	AAV (GPA, MPA, EGPA)	Worldwide
<i>RING</i>	rs213210, rs213209, and rs213208	GPA	German
<i>RXRB</i>	rs6531	GPA	German
<i>CD226</i>	rs763361	GPA	German
<i>CTLA4</i>	rs3087243, CT60	GPA, MPA and EGPA	British, Swedish
<i>DEFB4</i>	High CNVs	AAV	Chinese
<i>DSP</i>	rs2076295G	MPA	Japanese
<i>ETS1</i>	rs1128334	GPA	Japanese
<i>FCGR3B</i>	Low CNVs, High CNVs	AAV	French, British, Chinese
<i>IL10</i>	IL10 -3575/-1082/-592 TAC haplotype	EGPA(ANCA-)	German
<i>IL2RA</i>	rs41295061	AAV	British
<i>MUC5B</i>	rs35705950	AAV-ILD	Japanese
<i>PTPN22</i>	rs2476601, C1858T	GPA, MPA	German, Italian, British
<i>TLR-9</i>	rs352162, rs352140, rs352139 CTC, TCT	GPA, MPA, EGPA	German, British, Dutch
<i>TERT</i>	rs2736100A	MPA	Japanese

All the genes associated with AAV were summarized in **Table 3**.

CONCLUSION

In the past 20 years, genetic studies, including GWAS and candidate gene studies, have identified numerous key loci that are associated with the risk of AAV. These genes have not only provided novel etiological clues to deepen our understanding of AAV but also novel therapeutic and prophylactic biomarkers for new approaches to treat and prevent AAV. Biomarker-targeting therapies and preventing recurrence in the future may be more effective. With the increasing number of GWAS being conducted, it is desirable to combine these findings and improve the statistical power. To date, GWAS for AAV have been performed in the European population; in the future, more GWAS with large samples in different populations and different subgroups of AAV are required to reveal the pathogenesis of the disease and identify reliable biomarkers for precision medicine.

AUTHOR CONTRIBUTIONS

YS is the investigator for the review article and has contributed to the concept and planning of the article, collection of data, and reporting of the work described. WL, HH, MC, and TY

contributed to the collection of data, and reporting of the work described. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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