

REVIEW

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# An immunogenetic perspective of ANCA-associated vasculitides

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## Abstract

**Background:** Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are a group of small vessel vasculitides characterized by necrotizing vasculitis and inflammation. The phenotypes of AAV include microscopic polyangiitis (MPA), granulomatosis and polyangiitis (GPA), and eosinophilic granulomatosis and polyangiitis (EGPA). The pathogenesis of AAV is multifactorial, and it is suggested that both genetic and environmental factors can influence these disorders.

**Main body:** Several candidate gene studies and genome-wide association studies (GWAS) have been conducted to investigate the genetic associations with AAV in recent years. Numerous genes have been related to the pathogenesis of AAV, including the innate, adaptive immune system and coagulation systems.

**Conclusion:** This review summarizes the immunological mechanisms involved in the etiopathogenesis of AAV and recent advances in susceptibility genes.

**Keywords:** ANCA-associated vasculitis, Genome-wide association study, Human leukocyte antigen, Immunogenetics, Polymorphism

## Background

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are primary systemic disorders that cause necrotizing inflammation of the small blood vessels such as arterioles, capillaries, and venules. The presence of anti-neutrophil cytoplasmic antibodies (ANCA) is a characteristic feature of ANCA-associated vasculitides [1]. This group includes granulomatosis with polyangiitis (GPA, formerly Wegener granulomatosis), microscopic polyangiitis (MPA), and eosinophilic GPA (EGPA, formerly Churg-Strauss syndrome) [2]. Although the prevalence of AAV varies by geographic region, GPA is more common in Europe, and MPA is more common in Asia [3]. MPA is more common in Southern European countries than in Northern European countries [4]. The

pathogenesis of AAV is still unknown. Various genetic, immunological, and micro- and macroenvironmental factors have been suggested to play a role in the development of AAV [5]. Infective triggers that facilitate neutrophil activation and increase migration of cytoplasmic PR3 and MPO antigens to the neutrophil surface may lead to disease onset [6, 7]. In this review, we will focus on the potential effects of polymorphisms in many genes involved in the immune response, which may play a role in the immunogenetic basis of AAV.

## Main text

### Human leukocyte antigen (HLA) genes

The MHC, also known as the human leukocyte antigen (HLA) region, encodes several molecules that play key roles in the immune system. HLA genes, including both class I (A, B, C) and class II (DR, DQ, and DP), have been associated with susceptibility to AAV [8]. Katz et al. showed an association between HLA-B\*08 and GPA [9]. One study demonstrated that the HLA-A\*01-B\*08-DRB1\*03 haplotype was more frequent in AAV

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patients compared to those with GPA [10]. The relationship between HLA class II genes and AAV shows divergent results across ethnic groups and geographic regions. Previous studies demonstrated that HLA-DPB1 was a major contributor to AAV genetic risk (particularly HLA-DPB1\*0401 in GPA) [11, 12]. The alleles of HLA-DRB1\*13 were found to be a protective factor for GPA in a Dutch cohort [13]. On the other hand, the alleles of HLA-DRB1\*04 have been found to be associated with GPA in Dutch patients [10]. The HLA-DBP1\*03:01 was found to be less common in GPA patients with + ANCA [14]. The G allele of HLA-DBP1 (rs3117242) has been shown to be a risk factor for GPA in Caucasian patients [11]. The HLA-DRB1\*15 was found to be linked with PR3-ANCA+ disease in a population of African-Americans [15]. In Japanese subjects, the HLA-DRB1\*09:01 was found to be associated with both MPA and MPO-ANCA [16]. The rs5000634 single nucleotide polymorphism (SNP) of HLA-DQB1 has also been associated with MPA in Caucasian patients [11]. In another study, HLA-DRB1\*08 alleles were found more frequently in EGPA patients compared to the control group [10]. Also, the HLA-DRB4 alleles were found to be related to symptoms of vasculitis in German patients [17]. In a recent study, the DRB1\*03 and DQB1\*02 alleles were associated with confirmed in proteinase 3 (PR3)-AAV patients, whereas the DRB1\*10, DRB1\*14, and DQB1\*05 were found to be protective alleles in AAV [18].

#### ANCA target proteins

Proteinase 3 (PR3) rs62132295 was found to be associated with PR3-ANCA+ [19]. In a German population, the -564 A/G SNP of the PR3 gene was associated with GPA [20]. The GG genotype of myeloperoxidase (MPO) 463 G/A was found to be associated with MPO-ANCA+ in female patients [21]. A recent meta-analysis showed no association between SNPs of the MPO gene and AAV [22]. Serpin family A member 1, encoding  $\alpha$ 1-antitrypsin (SERPINA1) protease inhibitor Z (PiZ), was found to be linked with AAV [23]. The S and Z alleles of SERPINA1 were related to GPA patients in a North American cohort [24]. However, this significant association was not found in a study with Chinese patients [25].

#### Co-stimulatory molecules and signaling regulators

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) gene plays a major role in T cell inhibition. The SNPs of CTLA-4 CT60 and CTLA-4 + 49 have been related to AAV susceptibility in European patients [26]. Another study demonstrated that the CTLA-4-318 SNP was associated with GPA susceptibility [27]. The GG genotype of CTLA-4 + 49A/G was found to be correlated with AAV (PR3-AAV and GPA) in an Indian cohort [18]. The

A allele of rs3087243 CTLA has been found to be a protective factor against AAV [28]. The association of programmed cell death 1 (PDCD1) SNPs with AAV alone has not been proven. The combination of CTLA-4 + 49 AA and PDCD-1.5 T SNP was found to be less frequent in patients with AAV compared to controls [27]. Cluster of differentiation 226 (CD226) is a receptor expressed by T cells, NK cells, and some B cells and plays a role in the cytolytic function of T cells [29]. The minor allele (Ser307) of the CD226 Gly307Ser was linked to GPA [30]. The protein tyrosine phosphatase non-receptor type 22 (PTPN22) gene encodes a protein tyrosine phosphatase that induces type I interferon. The R620W SNP of PTPN22 was found to be related to GPA ANCA+ in different studies [31, 32]. Moreover, the R620W polymorphism of PTPN22 has also been related to MPA susceptibility in a British population [28].

#### Cytokines and cytokine-related genes

Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) is a tissue damage mediator produced by T helper 17 (Th17) and macrophages in response to immune system activation. The TNF- $\alpha$ -238 SNP was found to be associated with GPA in German patients [33]. However, a meta-analysis showed that the TNF- $\alpha$ -308 SNP was not linked with AAV in Europeans [26]. The AA genotype of IL-10 (-1082) was found to be associated in female patients with MPA [34]. A CA repeat polymorphism of the IL-10 gene was associated with GPA [35]. The AA genotype of IL-10 (-1082) was found to be associated with GPA [34]. Wieczorek et al. observed that the IL-10.2 SNP was linked with ANCA-negative EGPA patients [36]. Interferon gamma (IFN- $\gamma$ ) is a mediator that induces pro-inflammatory IL-12 secretion and inhibits anti-inflammatory IL-10 production. IFN $\gamma$  (+874 T/T) and (+874 A/A) polymorphisms were found to be related to an overall increased risk of AAV [33]. IL2RA is the gene that encodes the alpha chain of the high-affinity IL-2 receptor, which is primarily expressed by T cells, activated B cells, activated monocytes, and NK cells [37]. In the study of Carr et al., it was demonstrated that the IL2RA rs41295061 polymorphism has been associated with AAV in British patients [38]. The leptin/ghrelin system is two mediators with opposing effects in the regulation of the immune system. The 656Lys allele has been shown to be associated with high EGPA and low GPA risk [39]. Interferon regulatory factor 5 (IRF5) is a gene that stimulates the expression of type I interferon, IL-6, IL-12, and TNF- $\alpha$  and is expressed by B cells and monocytes. The rs2004640-G/Exon6-ins/rs2070197-T/rs10954213-G haplotype has been found to be a protective factor in GPA patients [40]. The T allele of rs35705950 oligomeric mucus/gel-forming (MUC5B) was found to be related with AAV susceptibility [41]. ETS

proto-oncogene 1 is a transcription factor that affects the expression of cytokine and chemokine genes and plays a role in various immune responses. A study with a Japanese population showed that ETS1 polymorphism was found to be associated with GPA [42]. In a study conducted by Kawasaki et al., the telomerase reverse transcriptase (TERT) rs2736100A and Desmoplakin rs2076295G were associated with MPA and MPO-AAV [43]. Haplotypes 1 and 4 of glucocorticoid receptor and 11 $\beta$ -hydroxysteroid dehydrogenase type 1 gene were associated with clinically relevant inflammatory and metabolic outcomes in ANCA-associated vasculitis [44]. The A/A genotype at position -2518 in the monocyte chemoattractant protein-1 (MCP-1) was associated with a poor prognosis in Swedish patients with AAV [45].

### Fc receptors

Receptors for IgG on leucocytes (Fc $\gamma$ R) bind to the Fc-part of IgG and serve as a link between the humoral and cellular parts of the immune system [46]. Fc $\gamma$ R is divided into three main classes: Fc $\gamma$ RI (CD64), Fc $\gamma$ RII (CD 32), and Fc $\gamma$ RIII (CD16). Fc $\gamma$ RI facilitates antigen presentation to T cells, and Fc $\gamma$ RIIa induces degranulation and phagocytosis. Fc $\gamma$ RIIb mediates downregulation of antibody responses [47]. The Fc $\gamma$ R IIIa-V/V158 SNP was found to be related to GPA predisposition. In addition, patients with both R/R131 homozygous for Fc $\gamma$ R IIa and F/F158 homozygous for Fc $\gamma$ R IIIa were more prone to disease relapse than the other groups [48]. The Fc $\gamma$ R IIIb homozygous allele NA1 was related to MPO-ANCA+ in Caucasian patients with AAV [49]. The Fc $\gamma$ R IIIb polymorphism was not associated with GPA, but the frequency of this SNP was found higher in patients with renal involvement compared to those without [50]. The A allele of Fc $\alpha$  receptor (FCAR) rs16986050 was associated with a higher susceptibility to GPA. However, the G allele was shown to be more frequent in patients with renal involvement than in those without [50].

### Other receptors

CD18 is a  $\beta$ 2 integrin chain that contributes to chemotaxis, phagocytosis, and homotypic adhesion. The C44T, AvaII, and T-1G SNPs of the CD18 gene have been related with MPO-ANCA+, but not with PR3-ANCA+ [51]. Killer cell immunoglobulin-like receptors (KIRs) are important receptors that activate or inhibit NK cells by recognizing class I major tissue compatibility complex (MHC) molecules [52]. The frequency of HLA-Bw4 and KIR3DL1 was shown to be higher in MPA patients compared with controls [53]. Leukocyte immunoglobulin-like receptors (LILRs) are mainly expressed in myelomonocytic and B cells [54]. In a Japanese population, rs2241524

in the A allele of LILRA2 was found to be more common in MPA patients compared to controls [55].

### Other proteins

The alternative pathway of complement activation increases chemotaxis by activating neutrophils, and as a result, the development of AAV damage is facilitated [56]. The C3F allele was found to be related to PR3-ANCA+ in Swedish patients [57]. Although the C4A3 allele was found to be associated with susceptibility to AAV, it was not correlated with any clinical findings [57]. Defensins are antimicrobial peptidic components involved in a variety of immunomodulatory activities, including the recruitment of adaptive and innate immune cells [58]. Human neutrophil peptides ( $\alpha$ -defensin) and human  $\beta$ -defensin 2 (DEFB4) were demonstrated to be related to GPA susceptibility [59]. GPA patients have been shown to have a higher DEFB4 gene copy number than controls [60]. COL11A2 gene encodes the  $\alpha$ 2(XI) chain of type XI collagen, it is expressed in the inner ear and the nucleus pulposus intervertebral discs. Lyons et al. showed that the rs3130233 and rs3117016 polymorphisms of COL11A2 were found to be related to AAV [11].

### Somatic cell mutations

Somatic UBA1, an X-chromosome gene encoding ubiquitin-like modifier-activating enzyme 1, gene mutations are related to vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome. The VEXAS syndrome was identified in patients with cytopenias, dysplastic bone marrow, vasculitis, and pulmonary inflammation [61]. The majority of patients have somatic missense mutations in UBA1 that affect p.Met41Leu [62].

### Conclusions

The AAV is a systemic small vessel vasculitis characterized by the presence of autoantibodies that recognize neutrophil cytoplasmic antigens. The mechanisms by which neutrophil expression of these species cause autoimmunity are not yet known. Although a combination of genetic predisposition and environmental factors has been suggested to cause the disease in patients with AAV, convincing data to support this is still inconclusive. In recent years, genetic factors that predispose to ANCA development have been better understood through genome-wide association studies and candidate gene studies. The results of genome-wide association studies of AAV demonstrated that HLA DBP1 (rs3117242), proteinase 3 (rs62132295), and SERPINA1 (rs715156) SNPs were related to PR3-ANCA+. Furthermore, these SNPs were found to be associated with PR3-ANCA+ in patients with MPA. Other genetic polymorphisms, such as CTLA4, IRF5, MUC5B, PTPN22, ETS1, and TERT,

were also likely to be contributory to AAV. This article provides a review of the relevant literature to determine the genetic basis of AAV. We believe that elucidating the immunogenetics of AAV will lead to the identification of biomarkers to be used in disease progression and possibly the discovery of new therapeutic targets.

#### Abbreviations

AAV: Anti-neutrophil cytoplasmic antibodies-associated vasculitides; ANCA: Anti-neutrophil cytoplasmic antibody; CD: Cluster of differentiation; COL11A2: Collagen type XI alpha 2 chain; CTL4: Cytotoxic T-lymphocyte associated protein 4; EGPA: Eosinophilic granulomatosis with polyangiitis; ETS1: ETS proto-oncogene 1, transcription factor; FCAR: Fc $\alpha$  receptor; GPA: Granulomatosis with polyangiitis; GWAS: Genome-wide association study; HLA: Human leukocyte antigen; IFN: Interferon; IFN- $\gamma$ : Interferon gamma; IL: Interleukin; IRF5: Interferon regulatory factor 5; KIRs: Killer cell immunoglobulin-like receptors; LILRs: Leukocyte immunoglobulin-like receptors; MCP-1: Monocyte chemoattractant protein-1; MHC: Major histocompatibility complex; MPA: Microscopic polyangiitis; MPO: Myeloperoxidase; MUC5B: Mucin 5B, oligomeric mucus/gel-forming; PDCD1: Programmed cell death 1; PiZ: Protease inhibitor Z; PR3: Proteinase 3; PTPN22: Protein tyrosine phosphatase non-receptor type 22; SERPINA1: Serpin family A member 1; TERT: Telomerase reverse transcriptase; Th17: T helper 17; TNF: Tumor necrosis factor; UBA1: Ubiquitin-like modifier-activating enzyme 1; VEXAS: Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic.

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#### Authors' contributions

Conceptualization: A.K and M.K. Writing original draft preparation: A.K. Writing, review, and editing: A.K and M.K. Visualization: M.K. Supervision: A.K and M.K. All authors have read and agreed to the published version of the manuscript.

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#### Competing interests

The authors declare that they have no competing interests.

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