

# Genetics of ANCA-associated Vasculitides

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**Abstract** The distribution of the anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV) is not uniform across geographical regions and ethnic and racial groups, suggesting that genetic and environmental factors affect the pathogenesis of these diseases. In addition, genetic factors affect not only the clinical syndrome phenotypes and their prognosis, but also ANCA specificity; these data suggest that AAV may need reclassification. Several genes have been evaluated, including ANCA targets and those of the immune system, for example co-stimulatory molecules, signaling regulators, cytokines, Fc and other receptors, and other proteins. This article provides a review of genetic factors affecting the pathogenesis and prognosis of AAV. Further studies to determine the effect of genetic factors on the clinical syndrome phenotypes and ANCA specificity need to be performed across different ethnic groups.

**Keywords** Anti-neutrophil cytoplasmic antibody-associated vasculitis · ANCA · Genetics · Vasculitides · Microscopic polyangiitis · Granulomatosis and polyangiitis · Eosinophilic granulomatosis and polyangiitis · HLA

## Introduction

Anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV) are a group of diseases which usually involve small-sized vessels. This group includes microscopic polyangiitis (MPA), granulomatosis and polyangiitis (GPA), and eosinophilic granulomatosis and polyangiitis (EGPA). MPA and EGPA are mainly associated with myeloperoxidase (MPO) ANCA, and GPA is associated with proteinase-3 (PR3) ANCA. These AAV are characterized by necrotizing vasculitis with reduced immune complexes, in association with ANCA [1].

The prevalence of these disorders varies with geographical region, GPA being more frequent in Europe, and MPA more frequent in Asia [2]. Among European countries, those in the Mediterranean region have a higher prevalence of MPA than those in Northern Europe [3]; in the Americas, North Americans have a higher prevalence of GPA, and South Americans of MPA [1]. This latitudinal gradient could reflect a mixture of genetic and environmental factors in the pathogenesis of AAV.

In this review, we will focus on the genetic basis of AAV and the potential effect of these polymorphisms. An overview of genes included in this review is presented in Table 1.

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## Human Leukocyte Antigen (HLA) Region

### HLA

HLA genes, including both class I and class II, have been associated with susceptibility to AAV (for this review, articles with HLA reported as serologically defined are expressed as their equivalent DNA-defined group). Among the HLA class I genes, Katz et al. found an association between *HLA-B\*08* and GPA [4]; also, the *HLA-A\*01-B\*08-DRB1\*03* haplotype

**Table 1** Genes associated with ANCA-associated vasculitis

Group	Gene	Disease	Country or region
HLA region			
HLA	HLA class I [4]	GPA	US
	HLA class II [5–10, 11••, 13, 15–20]	AAV (GPA, MPA, EGPA)	Worldwide
	RXRβ [8, 21, 22]	GPA	Germany
	RING [9]	GPA	Germany
ANCA specificity			
PR3 related	PRTN3 [11••, 26]	AAV (Mainly PR3+)	Europe
	α1 antitrypsin [11••, 38, 39, 41]	GPA	Europe, US
Co-stimulatory and signaling regulator			
Co-stimulatory molecules	CTLA-4 [45••, 46, 49]	AAV	UK, Netherlands
	CTLA-4+PD-1 [47]	AAV	Netherlands
	CD226 [52]	GPA	Germany
Signaling regulator	PTPN22 [49, 54, 55••, 56]	GPA, MPA	Europe
Cytokine and cytokine-related molecules			
Cytokines	TNF-α [48]	GPA	Germany
	IL-1 [58]	PR3-ANCA+with ESRD	Germany
	IL-10 [60–62]	GPA, MPA, EGPA	Germany, Sweden
	IFNγ [48]	GPA	Germany
Cytokine receptor	IL-2RA [66]	AAV	UK
Other molecules	Leptin [68]	GPA, EGPA	Germany
Regulatory factor	IRF5 [70]	GPA	Germany
Immune complex clearance			
Phagocytic	FcγR IIa and FcγR IIIa [73]	GPA	Netherlands
	FcγR IIIb [78]	MPO-ANCA+	UK
	FcαR [79]	GPA	US
Other receptors	CD18 [83, 84]	MPO-ANCA+	Germany
	KIR [86]	MPA	Japan
	LILR [88]	MPA	Japan
Other proteins			
Complement	C3 [89, 90]	PR3-ANCA+	Sweden
	C4 [90]	AAV	Sweden
Defensins	B Defensin 2 [92, 94]	GPA	China
Collagen	Collagen XI [9, 11••]	AAV	Europe

AAV, ANCA associated vasculitides; MPA, microscopic polyangiitis; GPA, granulomatosis and polyangiitis; EGPA, eosinophilic granulomatosis and polyangiitis; HLA, human leukocyte antigen; RXRβ, retinoid X-receptor beta; RING, ring finger protein 1; PR3, proteinase 3; TNF, tumor necrosis factor; IL, interleukin; IFN, interferon; IRF, interferon regulatory factor; FcγR, FcγReceptor; FcαR, FcαReceptor; KIR, killer-cell immunoglobulin-like receptors; LILR, leukocyte immunoglobulin-like receptor

is more frequent in AAV patients, mainly in those with GPA [5].

The association between HLA class II genes and specific clinical syndromes or ANCA specificities varies between ethnic groups and geographical regions; almost all studies focus mainly on patients with GPA and MPA.

Alleles of *HLA-DRB1\*13* were found to be protective for Dutch GPA patients [5, 6] and PR3-ANCA+German GPA patients [7]. *HLA-DBP1\*03:01* was less frequent in GPA patients, in particular those who were ANCA+[8, 9]. *HLA-*

*DQB1\*06:03* was also found to be protective for PR3-ANCA+patients [7]. On the other hand, alleles of *HLA-DRB1\*04* have been found to be related to GPA in Dutch patients [5], and to be associated with end-stage renal disease (ESRD) in German PR3-ANCA+patients [7]. *HLA-DBP1\*04:01* is more frequent in UK and German GPA patients [8, 10]. A polymorphism of *HLA-DBP1*, rs3117242 (G), has been associated with GPA, mainly in PR3-ANCA+Caucasian patients [11••]. In the US, *HLA-DRB1\*15* is associated with PR3-ANCA+disease, particularly among African-

Americans [12], and *HLA-DRB1\*12:02* is associated with GPA PR3-ANCA+ in Chinese patients [13]. The data on *HLA-DRB1\*01* are controversial [5, 14].

Among MPA patients, *HLA-DRB1\*09:01* has been associated with MPA and MPO-ANCA in Japanese patients [15], and the haplotype *DRB1\*09:01-DQB1\*03:03* has been associated with MPA [16]. In Chinese patients, *HLA-DRB1\*11:01* has been associated with MPA. A polymorphism of *HLA-DQB1*, rs5000634, has also been associated with MPA, mainly in MPO-ANCA+ Caucasian patients [11••].

HLA polymorphisms have also been associated with the severity and prognosis of AAV: *HLA-DRB1\*04:05* was found to be associated with worse renal prognosis and poorer response to treatment, whereas *HLA-DRB1\*04:02* was found to be associated with higher mortality in a study conducted in China [17]. *HLA-DRB1\*15* has been associated with more severe disease and *HLA-DRB1\*05* with renal disease in Brazilian patients with MPA [18].

There are a few studies of EGPA patients, mainly conducted on Caucasian patients. In a Dutch study alleles of *HLA-DRB1\*08* were found more frequently in EGPA patients [5], and in an Italian study alleles of *HLA-DRB4* and, in particular, *HLA-DRB1\*07*, were more frequent among patients with EGPA, whereas alleles of *HLA-DRB3* were less frequent. In addition, *HLA-DRB4* alleles were associated with a higher number of vasculitis symptoms [19]; these results were confirmed in German patients [20].

#### Retinoid X Receptor Beta (RXRB)

The RXRB receptor forms homodimers or heterodimers with retinoid acid, thyroid hormone, or vitamin D receptor, regulating their effects [21]. Because *RXRB* is in the HLA region of the genome near *HLA-DPB1*, it has been proposed that an *HLA-DPB1\*/RXRB* haplotype could be associated with an increased risk of GPA. The allele 01 of RXRB and the *HLA-DPB1/RXRB \*0301/01* haplotype are associated with a reduced risk of GPA, whereas the *HLA-DPB1/RXRB \*0401/03* haplotype is associated with a higher risk [8]. A single nucleotide polymorphism (SNP) of RXRB (rs6531) is increased among ANCA+GPA patients; in addition, the SNP rs10548957 has a marginal positive association with GPA [22]. Dinucleotide repeats have also been evaluated, revealing the distribution of seven alleles to differ between AAV patients and controls [21]. In addition, exon 7 SNPs affect the action of vitamin D and retinoid acid on IL-10 production among AAV patients, but have no effect on overall disease risk [21].

#### Ring Finger Protein 1 (RING)

RING is a member of polycomb-repressive complex 1 that mediates histone H2A polyubiquitination and

monoubiquitination, regulating its gene expression [23]. The human multimeric polycomb group can also act as a repressor of gene activity [24]. RING is also located in the HLA region of the genome, near *HLA-DPB1*; because of this, its polymorphism could be associated with an increased risk of GPA. There are three SNPs in the region surrounding RING1 (rs213210, rs213209, and rs213208) which have been found to be associated with GPA in German patients. However, this association is not related to *HLA-DPB1* [9].

### ANCA Target Proteins

#### PR3 Gene (PRTN3)

The PRTN3 SNP -564 A/G is associated with the binding site of transcription factor SP1; however, its effect in increasing promoter activity is still controversial [25].

PRTN3 SNP (rs62132295) is associated with AAV, mainly with PR3-ANCA+ [11••] and a SNP, -564 A/G, has been associated with GPA [26], albeit not consistently [27].

#### MPO

The -463 G/A SNP is associated with the function of the SP1 transcription-binding site. The GG polymorphism is within the SP1 transcription-binding site, retinoid-acid receptor, and thyroid-hormone receptor [28]. The AA polymorphism, however, abolishes SP1 binding, generating an estrogen-receptor binding site [29].

The GG polymorphism is more frequent in female MPO-ANCA+ patients. This polymorphism has been found to be associated with less frequent involvement of the upper respiratory tract and more relapse-free survival [30], but the effect of MPO polymorphisms on AAV pathogenesis is still controversial [31]. A recent meta-analysis could not prove an association between MPO polymorphisms and AAV susceptibility; however, the possibility of a type II error could not be excluded in this study [32].

#### Alpha-1 Antitrypsin ( $\alpha$ 1-AT)

Alpha-1 antitrypsin ( $\alpha$ 1-AT), the most abundant protease inhibitor in plasma, is a member of the serine protease inhibitor family (serpins), and inactivates PR3 and elastase. Because of this function, it has been proposed that deficiency or inactivation of  $\alpha$ 1-AT could be related to AAV, mainly GPA [33].

Alpha-1 antitrypsin is encoded by a highly polymorphic gene with at least 200 genetic variants [34]. One of these, *SERPINA1 PiZ* (protease inhibitor Z), has been associated with AAV [35], mainly in PR3-ANCA+ patients [36, 37]

and GPA patients [11••, 38, 39], and also with worse prognosis [40]. However, it seems not to be associated with MPA [39]. The PiZ homozygote is associated with a severely deficient  $\alpha$ 1-AT phenotype; and a moderately deficient  $\alpha$ 1-AT phenotype has been associated with PR3-ANCA+ [36]. In US patients, alleles S and Z (both of them alleles of  $\alpha$ 1-AT deficiency) are associated with GPA [41]. Alleles S and Z seem to have a different effect on the pattern of ANCA; in a study from the United Kingdom, cytoplasmic ANCA was found to be associated with the Z allele whereas perinuclear ANCA was found to be associated with the S allele [42]. However, these associations could not be observed in a study from China [43].

Another serpin, alpha-1 antichymotrypsin (AACT), does not seem to be associated with PR3-ANCA+ [44].

### Co-Stimulatory Molecules and Signaling Regulators

#### CTLA-4

CTLA-4 is a negative regulator of T-cell activation. Several polymorphisms of CTLA-4 have been evaluated in AAV patients; of these, a 3'-end AT(n) repeat length of 86 bp is protective compared with alleles with more than 86 bp. This association has mainly been evaluated in European patients [45••]. The CTLA-4 CT60 and CTLA-4+49 SNPs have also been associated with AAV in European patients [45••]. The CTLA-4 -318 SNP has been associated with GPA [46], albeit not consistently [47]. This SNP could be associated with prognosis (ESRD) and not necessarily with susceptibility [48]. Finally, SNP rs3087243 (A allele) has been found to be protective against AAV [49].

#### PD-1

*PDCD1* is the gene that encodes PD-1, a negative regulator of T-cells; PD-1 and its ligand PD-L1 induce expression of regulatory T cells and reduce expression of auto-reactive T cells [50]. An association of *PDCD1* SNP with AAV has not been proved; however, CTLA-4+49 AA SNP combined with *PDCD1.5* T SNP has been found to be less frequent among patients with AAV than among controls [47]. This suggests that a combination of mutations in more than one regulatory molecule could increase the risk of AAV.

#### CD226

CD226 is a surface receptor with a co-stimulatory function, expressed in T cells, NK cells, and some B cells [51]. It is involved with the cytolytic function of T cells [51]. The minor allele (ser307) of the CD226 Gly307Ser SNP is associated

with GPA [52]. The exact functional consequence of this polymorphism is yet to be elucidated.

#### PTPN22

PTPN22 is expressed in several immune cells, including T cells, B cells, NK cells, dendritic cells, and monocytes modulating immune response [53]. The PTPN22 (R620W) [49, 54, 55••, 56] SNP is associated with AAV, mainly with GPA and in particular with ANCA+ [55••, 56]. The R620W SNP has also been associated, although not consistently, with systemic involvement [56] and granulomatous manifestations [55••]. Polymorphism of PTPN22 (R620W) has also been associated with MPA [49].

### Cytokines and Cytokine-Related Genes

#### Tumor Necrosis Factor- $\alpha$ (TNF- $\alpha$ )

TNF- $\alpha$  has been implicated in several AAV pathogenic events. TNF- $\alpha$  primes neutrophils for the surface display of ANCA antigens, and is also produced by Th17 and macrophages as consequence of immune system activation and is one of the mediators of tissue damage [57]. TNF- $\alpha$  -308 SNP has not been associated with AAV [45••]; however, TNF- $\alpha$  -238 SNP has been associated with GPA [48].

#### Interleukin-1 (IL-1)

A proinflammatory genotype (A2+), characterized by high secretion of IL-1 $\beta$  and low secretion of IL-1 receptor antagonist (IL-1ra), is associated with ESRD in PR3-ANCA+ patients [58]. However, none of these polymorphisms have been found to be associated with an overall susceptibility to AAV or ESRD in MPO-ANCA+ patients [58].

#### IL-10

There are several SNPs associated with IL-10 function; of them, a G allele at position -1082 seems to be the most important genetic factor associated with higher production of IL-10 [59]. AA IL-10 (-1082) SNP has also been associated with MPA, but only in female patients [60]. A SNP of IL-10 (IL-10.G 134/136) has been associated with GPA [61], and another SNP, AA IL-10 (-1082), has been associated with GPA [60]; however, this latter association is still controversial [48, 62]. A combination of SNP of IL-10 (-1082, -819, -592; GCC/ACC) is associated with less frequent ESRD than is GCC/GCC [48]; the GCC/GCC variant is associated with higher production of IL-10 [59]. Finally, the IL-10.2 SNP has been associated with ANCA-negative EGPA patients [62].

## IFN $\gamma$

A SNP of IFN $\gamma$  (+874 T) has been associated with increased expression of this cytokine, whereas +874 A has been associated with reduced expression [63]. IFN $\gamma$  (+874 T/T) has been found to be associated with an overall increased risk of GPA. However, in the same patients, another SNP (+874 A/A) was found to be associated with ESRD [48]. These data suggest a possible dual function of IFN $\gamma$  in the pathogenesis of GPA.

## IL2RA

IL2RA codifies the alpha chain of the high-affinity IL-2 receptor that is expressed mainly in T regs and can also be expressed by effector T cells, immature B cells, and other non-immune cells [64, 65]. The IL2RA SNP rs41295061 has been found to be associated with AAV among UK patients [66].

## Leptin

The leptin/ghrelin system has a function in regulation of the immune system; leptin induces immune responses (increase of IL-1 $\beta$ , IL-6, and TNF- $\alpha$ ), and ghrelin has the opposite effect [67]. Several leptin-receptor (LEPR) SNPs have been evaluated regarding AAV. Of these, the 656Lys allele is associated with a reduced risk of GPA but with a higher risk of EGPA [68]. Further evaluation is required to elucidate the effect of this polymorphism on the immune response.

## Interferon Regulatory Factor 5 (IRF5)

IRF5 has been associated with several autoimmune diseases, possibly because it participates in several signaling cascades. IRF5 is expressed on plasmacytoid dendritic cells, monocytes, and B cells, stimulating expression of type I interferon, IL-6, IL-12, and TNF- $\alpha$  [69]. Among GPA patients, the rs2004640-G/Exon6-ins/rs2070197-T/rs10954213-G haplotype has been found to be protective, mainly for those patients with systemic involvement [70]. The exact function of this haplotype needs to be elucidated.

## Fc Receptors

### Fc $\gamma$ Receptor (Fc $\gamma$ R)

Fc $\gamma$ R IIa polymorphism has not been found to be associated with AAV in Caucasian patients [71, 72]. However, Fc $\gamma$ R IIa-H/H131 combined with Fc $\gamma$ R IIIa-V/V158 was found to be enriched in patients with GPA compared with controls [73]. In addition, patients who were both homozygous R/R131 for Fc $\gamma$ R IIa and homozygous F/F158 for Fc $\gamma$ R IIIa were more prone to disease relapses compared with patients with another

combination of Fc $\gamma$ R phenotypes [73]. These associations could be explained by the affinity of IgG for these polymorphisms; the homozygous H/H131 for Fc $\gamma$ R IIa can bind IgG2, whereas the homozygous R/R131 for Fc $\gamma$ R IIa cannot [74]. The homozygous V/V158 (also known as V/V176 when the leader sequence is included) Fc $\gamma$ R IIIa can bind IgG1 and IgG3 more efficiently than can homozygous F/F158 Fc $\gamma$ R IIIa (also known as F/F176 when the leader sequence is included) [75]. The association of these two polymorphisms (Fc $\gamma$ R IIa-H/H131 and Fc $\gamma$ R IIIa-V/V158) may lead to more efficient phagocytosis and higher cell activation [73]. In contrast, the low-binding alleles of these two receptors could be associated with relapse caused by less efficient phagocytosis of *Staphylococcus aureus*, which can be opsonized by IgG2 [76].

The Fc $\gamma$ R IIIb allele NA1 is associated with a higher level of phagocytosis [77]. Fc $\gamma$ R IIIb homozygous allele NA1 is associated with MPO-ANCA+ in Caucasian patients with AAV [78]; this polymorphism does not seem to be associated with overall GPA susceptibility, but it is more frequent in patients with severe renal involvement [79].

### Fc $\alpha$ Receptor (Fc $\alpha$ R)

Polymorphisms of Fc $\alpha$ R seem to be related to disease susceptibility and organ involvement among GPA patients. Alleles of a SNP in FCAR, rs16986050 lead to two possible polymorphisms at codon 248; an A allele, which leads to less intense immune activation, and a G allele, which leads to increased cellular activation [80]. The A allele seems to be associated with a higher susceptibility to GPA; however, the G allele seems to be more frequent in patients with kidney involvement than in those without it [79]. These associations could be a result of the dual function of this receptor as an inhibitory–activating receptor [81].

## Other Receptors

### CD18

CD18 is the  $\beta$ 2 chain of integrins, and it is part of four leukocyte-restricted integrins; these integrins are involved in chemotaxis, phagocytosis, and homotypic adhesion [82]. CD18 polymorphisms (AvaII [83], C44T, and T-1G [84]) have been associated with MPO-ANCA+, but not with PR3-ANCA+.

### Killer-Cell Immunoglobulin-Like Receptors (KIRs)

KIRs are a family of highly polymorphic activating and inhibitory receptors; their ligands are MHC class I molecules. They are regulators of NK and a subset of T cells [85]. The frequency of subjects who carry HLA-Bw4 and inhibitory

KIR3DL1 but who do not express activating KIR3DS1 is increased among MPA patients compared with controls. This combination is supposed to be the most inhibitory combination, and because of that, this polymorphism suggests that ineffective clearance of pathogens could be one of the pathways of the pathogenesis of MPA [86].

#### Leukocyte Immunoglobulin-Like Receptor (LILR)

LILR can be divided into two main groups: LILRA, which associates with the Fc $\epsilon$ RI $\gamma$  adaptor protein which transduces signals through their activator domains; and LILRB, which has its own inhibitory domain. LILR are mainly expressed in myelomonocytic and B cells [87]. The SNP LILRA2 rs2241524 alleles A/A are more frequent in MPA patients than in controls [88]. LILRA2 has several functions, including suppression of dendritic-cell maturation and antigen presentation [87]. The exact effect of this polymorphism on pathogenesis of MPA needs to be elucidated.

#### Other Proteins

##### Complement

Complement activation, in particular the alternative pathway, is an important mediator of injury in AAV, activating neutrophils and stimulating chemotaxis; ANCA-activated neutrophils release complement-activating factor [57]. The C3F allele is found more frequently among PR3-ANCA+ patients than among controls [89, 90]. The frequency of C4A3 allele is increased among AAV patients, but no specific association with any clinical syndrome or ANCA-specificity has been found [90].

##### Defensins

Defensins are peptidic components of innate immunity which have antimicrobial functions and several immune regulatory activities, including maturation of dendritic cells and recruitment of adaptive and innate immune cells [91]. Human neutrophil peptides ( $\alpha$ -defensin) and human  $\beta$ -defensin 2 (hBD2 or DEFB4) are increased among GPA patients compared with controls [92]. The copy number in  $\beta$ -defensin gene correlates with its expression [93]. GPA patients have a higher DEFB4 gene-copy number than controls [94].

##### Collagen

COL11A2 encodes a component of collagen XI; it is expressed in hyaline cartilage, vitreous body, the nucleus pulposus of intervertebral discs, and in the inner ear.

COL11A2 SNP (rs58554423 [9], rs3130233, and rs3117016 [11••]) seems to be related to AAV, probably via linkage disequilibrium.

#### Genetic Risk Factors for Clinical Syndromes or ANCA Specificities?

Whether the association is between polymorphisms and clinical syndrome or between polymorphisms and ANCA specificity is still controversial. In the largest genome-wide association study of AAV, performed on a predominantly Caucasian population, HLA DBP1 (rs3117242), SERPINA1 (rs715156), and PRTN3 (rs62132295) SNPs were more strongly associated with PR3-ANCA+ than with GPA, whereas the HLA DQ (rs5000634) SNP was more strongly associated with MPO-ANCA+ than with MPA [11••]. In addition, polymorphisms of HLA DBP1 (rs3117242), SERPINA1 (rs715156), and PRTN3 (rs62132295) are associated with PR3-ANCA+ in patients with MPA and are not associated with MPO-ANCA+ in patients with GPA; and HLA DQ (rs5000634) polymorphism is associated with MPO-ANCA+ in patients with GPA, but not with PR3-ANCA+ in patients with MPA [11••]. These results suggest that genetic background could affect more ANCA specificities than it does clinical syndromes.

#### Conclusions

In this article, we have attempted to provide a broad overview of several studies that have been performed to determine the genetic background of AAV. Current data suggest that the genetic background could affect not only clinical syndromes but also ANCA specificity. Debate regarding whether AAV are one entity or multiple individual diseases, and the effect of ANCA specificity on disease classification, is ongoing. Further studies should clarify these important matters.

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#### Compliance With Ethics Guidelines

**Conflict of Interest** Manuel F. Ugarte-Gil and Luis R. Espinoza declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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