Curr Rheumatol Rep (2014) 16:428
DOI 10.1007/s11926-014-0428-5

VASCULITIS (LR ESPINOZA, SECTION EDITOR)

Genetics of ANCA-associated Vasculitides

Manuel F. Ugarte-Gil · Luis R. Espinoza

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

This article is part of the Topical Collection on *Vasculitis*

M. F. Ugarte-Gil (✉)
Servicio de Reumatología, Hospital Nacional Guillermo Almenara Irigoyen, EsSalud, Lima, Perú
e-mail: manuel_ugarte@yahoo.com

M. F. Ugarte-Gil
Universidad Científica del Sur, Lima, Perú

L. R. Espinoza
Louisiana State University Health Sciences Center, 433 Bolivar St, New Orleans, LA 70112, USA

Published online: 15 May 2014

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.

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
	RXRB [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; RXRB, 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-DBP1*/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 polyubiquination and monoubiquination, 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 SNP 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 (α1-AT)

Alpha-1 antitrypsin (α1-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 α1-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 α1-AT phenotype; and a moderately deficient α1-AT phenotype has been associated with PR3-ANCA+[36]. In US patients, alleles S and Z (both of them alleles of α1-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 PDCD-1.5 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-α (TNF-α)

TNF-α has been implicated in several AAV pathogenic events. TNF-α 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-α -308 SNP has not been associated with AAV [45••]; however, TNF-α -238 SNP has been associated with GPA [48].

Interleukin-1 (IL-1)

A proinflammatory genotype (A2+), characterized by high secretion of IL-1β 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].

IFNγ

A SNP of IFNγ (+874 T) has been associated with increased expression of this cytokine, whereas +874 A has been associated with reduced expression [63]. IFNγ (+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 IFNγ 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-1β, IL-6, and TNF-α), 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-α [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

FcγReceptor (FcγR)

FcγR IIa polymorphism has not been found to be associated with AAV in Caucasian patients [71, 72]. However, FcγR IIa-H/H131 combined with FcγR 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 FcγR IIa and homozygous F/F158 for FcγR IIIa were more prone to disease relapses compared with patients with another combination of FcγR phenotypes [73]. These associations could be explained by the affinity of IgG for these polymorphisms; the homozygous H/H131 for FcγR IIa can bind IgG2, whereas the homozygous R/R131 for FcγR IIa cannot [74]. The homozygous V/V158 (also known as V/V176 when the leader sequence is included) FcγR IIIa can bind IgG1 and IgG3 more efficiently than can homozygous F/F158 FcγR IIIa (also known as F/F176 when the leader sequence is included) [75]. The association of these two polymorphisms (FcγR IIa-H/H131 and FcγR 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 FcγR IIIb allele NA1 is associated with a higher level of phagocytosis [77]. FcγR 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].

FcαReceptor (FcαR)

Polymorphisms of FcαR 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 β2 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 FcεRIγ 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 (α-defensin) and human β-defensin 2 (hBD2 or DEFB4) are increased among GPA patients compared with controls [92]. The copy number in β-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 nucleous 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.

Acknowledgment The authors want to acknowledge Dr Graciela S. Alarcón from Department of Medicine, Division of Clinical Immunology and Rheumatology, School of Medicine, The University of Alabama at Birmingham, Birmingham, AL, USA for her critical review of this paper.

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.

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Gatenby PA. Anti-neutrophil cytoplasmic antibody-associated systemic vasculitis: nature or nurture? Intern Med J. 2012;42(9):1066–7. doi:10.1111/j.1445-5994.2012.02891.x.
2. Kobayashi S, Fujimoto S. Epidemiology of vasculitides: differences between Japan, Europe and North America. Clin Exp Nephrol. 2013;17(5):611–4. doi:10.1007/s10157-013-0813-9.
3. Watts RA, Gonzalez-Gay MA, Lane SE, Garcia-Porrua C, Bentham G, Scott DG. Geoepidemiology of systemic vasculitis: comparison of the incidence in two regions of Europe. Ann Rheum Dis. 2001;60(2):170–2.
4. Katz P, Alling DW, Haynes BF, Fauci AS. Association of Wegener's granulomatosis with HLA-B8. Clin Immunol Immunopathol. 1979;14(2):268–70.
5. Stassen PM, Cohen-Tervaert JW, Lems SP, Hepkema BG, Kallenberg CG, Stegeman CA. HLA-DR4, DR13(6) and the ancestral haplotype A1B8DR3 are associated with ANCA-associated vasculitis and Wegener's granulomatosis. Rheumatology (Oxford). 2009;48(6):622–5. doi:10.1093/rheumatology/kep057.
6. Hagen EC, Stegeman CA, D'Amaro J, Schreuder GM, Lems SP, Tervaert JW, et al. Decreased frequency of HLA-DR13DR6 in Wegener's granulomatosis. Kidney Int. 1995;48(3):801–5.
7. Gencik M, Borgmann S, Zahn R, Albert E, Sitter T, Epplen JT, et al. Immunogenetic risk factors for anti-neutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis. Clin Exp Immunol. 1999;117(2):412–7.
8. Jagiello P, Gencik M, Arning L, Wieczorek S, Kunstmann E, Csernok E, et al. New genomic region for Wegener's granulomatosis as revealed by an extended association screen with 202 apoptosis-related genes. Hum Genet. 2004;114(5):468–77. doi:10.1007/s00439-004-1092-z.
9. Heckmann M, Holle JU, Arning L, Knaup S, Hellmich B, Nothnagel M, et al. The Wegener's granulomatosis quantitative trait locus on chromosome 6p21.3 as characterised by tagSNP genotyping. Ann Rheum Dis. 2008;67(7):972–9. doi:10.1136/ard.2007.077693.
10. Arning L, Holle JU, Harper L, Millar DS, Gross WL, Epplen JT, et al. Are there specific genetic risk factors for the different forms of ANCA-associated vasculitis? Ann Rheum Dis. 2011;70(4):707–8. doi:10.1136/ard.2010.130971.
11.•• Lyons PA, Rayner TF, Trivedi S, Holle JU, Watts RA, Jayne DR, et al. Genetically distinct subsets within ANCA-associated vasculitis. N Engl J Med. 2012;367(3):214–23. doi:10.1056/NEJMoa1108735. *This article is the study with the biggest population, and found a greater association of genes with ANCA specificity than with clinical syndromes.*
12. Cao Y, Schmitz JL, Yang J, Hogan SL, Bunch D, Hu Y, et al. DRB1*15 allele is a risk factor for PR3-ANCA disease in African Americans. J Am Soc Nephrol. 2011;22(6):1161–7. doi:10.1681/ASN.2010101058.
13. Luo H, Chen M, Yang R, Xu PC, Zhao MH. The association of HLA-DRB1 alleles with antineutrophil cytoplasmic antibody-associated systemic vasculitis in Chinese patients. Hum Immunol. 2011;72(5):422–5. doi:10.1016/j.humimm.2011.02.017.
14. Papiha SS, Murty GE, Ad'Hia A, Mains BT, Venning M. Association of Wegener's granulomatosis with HLA antigens and other genetic markers. Ann Rheum Dis. 1992;51(2):246–8.
15. Tsuchiya N. Genetics of ANCA-associated vasculitis in Japan: a role for HLA-DRB1*09:01 haplotype. Clin Exp Nephrol. 2013;17(5):628–30. doi:10.1007/s10157-012-0691-6.
16. Tsuchiya N, Kobayashi S, Kawasaki A, Kyogoku C, Arimura Y, Yoshida M, et al. Genetic background of Japanese patients with antineutrophil cytoplasmic antibody-associated vasculitis: association of HLA-DRB1*0901 with microscopic polyangiitis. J Rheumatol. 2003;30(7):1534–40.
17. Chang DY, Luo H, Zhou XJ, Chen M, Zhao MH. Association of HLA genes with clinical outcomes of ANCA-associated vasculitis. Clin J Am Soc Nephrol. 2012;7(8):1293–9. doi:10.2215/CJN.13071211.
18. de Lira FA, Conde RA, Bertolo MB, Costallat LT, Levy-Neto M, Fernandes SR. HLA-DR in Brazilian patients with polyarteritis nodosa (PAN) and microscopic polyangiitis (MPA). Dis Markers. 2009;26(3):105–9. doi:10.3233/DMA-2009-0616.
19. Vaglio A, Martorana D, Maggiore U, Grasselli C, Zanetti A, Pesci A, et al. HLA-DRB4 as a genetic risk factor for Churg-Strauss syndrome. Arthritis Rheum. 2007;56(9):3159–66. doi:10.1002/art.22834.
20. Wieczorek S, Hellmich B, Gross WL, Epplen JT. Associations of Churg-Strauss syndrome with the HLA-DRB1 locus, and relationship to the genetics of antineutrophil cytoplasmic antibody-associated vasculitides: comment on the article by Vaglio et al. Arthritis Rheum. 2008;58(1):329–30. doi:10.1002/art.23209.
21. Kalsch AI, Peters A, Buhl B, Breedijk A, Prem K, Schmitt WH, et al. Retinoid X receptor beta polymorphisms do not explain functional differences in vitamins D and A response in Antineutrophil cytoplasmic antibody associated vasculitis patients. Autoimmunity. 2009;42(5):467–74.
22. Szyld P, Jagiello P, Csernok E, Gross WL, Epplen JT. On the Wegener granulomatosis associated region on chromosome 6p21.3. BMC Med Genet. 2006;7:21.
23. Ben-Saadon R, Zaaroor D, Ziv T, Ciechanover A. The polycomb protein Ring1B generates self atypical mixed ubiquitin chains required for its in vitro histone H2A ligase activity. Mol Cell. 2006;24(5):701–11. doi:10.1016/j.molcel.2006.10.022.
24. Satijn DP, Gunster MJ, van der Vlag J, Hamer KM, Schul W, Alkema MJ, et al. RING1 is associated with the polycomb group protein complex and acts as a transcriptional repressor. Mol Cell Biol. 1997;17(7):4105–13.
25. Pieters K, Pettersson A, Gullberg U, Hellmark T. The - 564 A/G polymorphism in the promoter region of the proteinase 3 gene associated with Wegener's granulomatosis does not increase the promoter activity. Clin Exp Immunol. 2004;138(2):266–70. doi:10.1111/j.1365-2249.2004.02608.x.
26. Gencik M, Meller S, Borgmann S, Fricke H. Proteinase 3 gene polymorphisms and Wegener's granulomatosis. Kidney Int. 2000;58(6):2473–7. doi:10.1046/j.1523-1755.2000.00430.x.
27. Abdgawad M, Hellmark T, Gunnarsson L, Westman KW, Segelmark M. Increased neutrophil membrane expression and plasma level of proteinase 3 in systemic vasculitis are not a consequence of the - 564 A/G promotor polymorphism. Clin Exp Immunol. 2006;145(1):63–70. doi:10.1111/j.1365-2249.2006.03119.x.
28. Piedrafita FJ, Molander RB, Vansant G, Orlova EA, Pfahl M, Reynolds WF. An Alu element in the myeloperoxidase promoter contains a composite SP1-thyroid hormone-retinoic acid response element. J Biol Chem. 1996;271(24):14412–20.
29. Reynolds WF, Hiltunen M, Pirskanen M, Mannermaa A, Helisalmi S, Lehtovirta M, et al. MPO and APOEepsilon4 polymorphisms interact to increase risk for AD in Finnish males. Neurology. 2000;55(9):1284–90.
30. Reynolds WF, Stegeman CA, Tervaert JW. 463 G/A myeloperoxidase promoter polymorphism is associated with clinical manifestations and the course of disease in MPO-ANCA-associated vasculitis. Clin Immunol. 2002;103(2):154–60. doi:10.1006/clim.2002.5206.

31. Fiebeler A, Borgmann S, Woywodt A, Haller H, Haubitz M. No association of G-463A myeloperoxidase gene polymorphism with MPO-ANCA-associated vasculitis. Nephrol Dial Transplant. 2004;19(4):969–71. doi:10.1093/ndt/gfh025.
32. Rajp A, Adu D, Savage CO. Meta-analysis of myeloperoxidase G-463/A polymorphism in anti-neutrophil cytoplasmic autoantibody-positive vasculitis. Clin Exp Immunol. 2007;149(2):251–6. doi:10.1111/j.1365-2249.2007.03418.x.
33. Esnault VL, Audrain MA, Sesboue R. Alpha-1-antitrypsin phenotyping in ANCA-associated diseases: one of several arguments for protease/antiprotease imbalance in systemic vasculitis. Exp Clin Immunogenet. 1997;14(3):206–13.
34. Bals R. Alpha-1-antitrypsin deficiency. Best Pract Res Clin Gastroenterol. 2010;24(5):629–33. doi:10.1016/j.bpg.2010.08.006.
35. Callea F, Gregorini G, Sinico A, Consalez GG, Bossolasco M, Salvidio G, et al. alpha 1-Antitrypsin (AAT) deficiency and ANCA-positive systemic vasculitis: genetic and clinical implications. Eur J Clin Invest. 1997;27(8):696–702.
36. Esnault VL, Testa A, Audrain M, Roge C, Hamidou M, Barrier JH, et al. Alpha 1-antitrypsin genetic polymorphism in ANCA-positive systemic vasculitis. Kidney Int. 1993;43(6):1329–32.
37. Savige JA, Chang L, Cook L, Burdon J, Daskalakis M, Doery J. Alpha 1-antitrypsin deficiency and anti-proteinase 3 antibodies in anti-neutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis. Clin Exp Immunol. 1995;100(2):194–7.
38. Elzouki AN, Segelmark M, Wieslander J, Eriksson S. Strong link between the alpha 1-antitrypsin PiZ allele and Wegener's granulomatosis. J Intern Med. 1994;236(5):543–8.
39. Morris H, Morgan MD, Wood AM, Smith SW, Ekeowa UI, Herrmann K, et al. ANCA-associated vasculitis is linked to carriage of the Z allele of alpha(1) antitrypsin and its polymers. Ann Rheum Dis. 2011;70(10):1851–6. doi:10.1136/ard.2011.153569.
40. Segelmark M, Elzouki AN, Wieslander J, Eriksson S. The PiZ gene of alpha 1-antitrypsin as a determinant of outcome in PR3-ANCA-positive vasculitis. Kidney Int. 1995;48(3):844–50.
41. Mahr AD, Edberg JC, Stone JH, Hoffman GS, St Clair EW, Specks U, et al. Alpha(1)-antitrypsin deficiency-related alleles Z and S and the risk of Wegener's granulomatosis. Arthritis Rheum. 2010;62(12):3760–7. doi:10.1002/art.27742.
42. Griffith ME, Lovegrove JU, Gaskin G, Whitehouse DB, Pusey CD. C-antineutrophil cytoplasmic antibody positivity in vasculitis patients is associated with the Z allele of alpha-1-antitrypsin, and P-antineutrophil cytoplasmic antibody positivity with the S allele. Nephrol Dial Transplant. 1996;11(3):438–43.
43. Lee SS, Lawton JW, Ko KH. Alpha1 antitrypsin phenotypic variability is not associated with ANCA in southern Chinese. Ann Rheum Dis. 2001;60(7):725–6.
44. Borgmann S, Haubitz M, Schwab SG. Lack of association of alpha-1 antichymotrypsin gene polymorphism with PR3-ANCA and MPO-ANCA associated vasculitis. Autoimmunity. 2002;35(7):435–9.
45.•• Lee YH, Choi SJ, Ji JD, Song GG. CTLA-4 and TNF-alpha promoter-308 A/G polymorphisms and ANCA-associated vasculitis susceptibility: a meta-analysis. Mol Biol Rep. 2012;39(1):319–26. doi:10.1007/s11033-011-0741-2. *This meta-analysis includes previous studies of CTLA-4 and TNF-alpha polymorphism and ANCA-associated vasculitis susceptibility, including mainly Caucasian patients.*
46. Giscombe R, Wang X, Huang D, Lefvert AK. Coding sequence 1 and promoter single nucleotide polymorphisms in the CTLA-4 gene in Wegener's granulomatosis. J Rheumatol. 2002;29(5):950–3.
47. Slot MC, Sokolowska MG, Savelkouls KG, Janssen RG, Damoiseaux JG, Tervaert JW. Immunoregulatory gene polymorphisms are associated with ANCA-related vasculitis. Clin Immunol. 2008;128(1):39–45. doi:10.1016/j.clim.2008.03.506.
48. Spriewald BM, Witzke O, Wassmuth R, Wenzel RR, Arnold ML, Philipp T, et al. Distinct tumour necrosis factor alpha, interferon gamma, interleukin 10, and cytotoxic T cell antigen 4 gene polymorphisms in disease occurrence and end stage renal disease in Wegener's granulomatosis. Ann Rheum Dis. 2005;64(3):457–61. doi:10.1136/ard.2004.025809.
49. Carr EJ, Niederer HA, Williams J, Harper L, Watts RA, Lyons PA, et al. Confirmation of the genetic association of CTLA4 and PTPN22 with ANCA-associated vasculitis. BMC Med Genet. 2009. doi:10.1186/1471-2350-10-121.
50. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev. 2010;236:219–42. doi:10.1111/j.1600-065X.2010.00923.x.
51. Shibuya A, Campbell D, Hannum C, Yssel H, Franz-Bacon K, McClanahan T, et al. DNAM-1, a novel adhesion molecule involved in the cytolytic function of T lymphocytes. Immunity. 1996;4(6):573–81.
52. Wieczorek S, Hoffjan S, Chan A, Rey L, Harper L, Fricke H, et al. Novel association of the CD226 (DNAM-1) Gly307Ser polymorphism in Wegener's granulomatosis and confirmation for multiple sclerosis in German patients. Genes Immun. 2009;10(6):591–5. doi:10.1038/gene.2009.44.
53. Fousteri G, Liossis SN, Battaglia M. Roles of the protein tyrosine phosphatase PTPN22 in immunity and autoimmunity. Clin Immunol. 2013;149(3):556–65. doi:10.1016/j.clim.2013.10.006.
54. Lee YH, Choi SJ, Ji JD, Song GG. The protein tyrosine phosphatase nonreceptor 22 C1858T polymorphism and vasculitis: a meta-analysis. Mol Biol Rep. 2012;39(8):8505–11. doi:10.1007/s11033-012-1705-x.
55.•• Martorana D, Maritati F, Malerba G, Bonatti F, Alberici F, Oliva E, et al. PTPN22 R620W polymorphism in the ANCA-associated vasculitides. Rheumatology (Oxford). 2012;51(5):805–12. doi:10.1093/rheumatology/ker446. *This meta-analysis includes previous studies of PTPN22 polymorphism and ANCA-associated vasculitis susceptibility, including mainly Caucasian patients.*
56. Jagiello P, Aries P, Arning L, Wagenleiter SE, Csernok E, Hellmich B, et al. The PTPN22 620W allele is a risk factor for Wegener's granulomatosis. Arthritis Rheum. 2005;52(12):4039–43. doi:10.1002/art.21487.
57. Jennette JC, Falk RJ, Hu P, Xiao H. Pathogenesis of antineutrophil cytoplasmic autoantibody-associated small-vessel vasculitis. Annu Rev Pathol. 2013;8:139–60. doi:10.1146/annurev-pathol-011811-132453.
58. Borgmann S, Endisch G, Hacker UT, Song BS, Fricke H. Proinflammatory genotype of interleukin-1 and interleukin-1 receptor antagonist is associated with ESRD in proteinase 3-ANCA vasculitis patients. Am J Kidney Dis. 2003;41(5):933–42.
59. Suarez A, Castro P, Alonso R, Mozo L, Gutierrez C. Interindividual variations in constitutive interleukin-10 messenger RNA and protein levels and their association with genetic polymorphisms. Transplantation. 2003;75(5):711–7. doi:10.1097/01.TP.0000055216.19866.9A.
60. Bartfai Z, Gaede KI, Russell KA, Murakozy G, Muller-Quernheim J, Specks U. Different gender-associated genotype risks of Wegener's granulomatosis and microscopic polyangiitis. Clin Immunol. 2003;109(3):330–7.
61. Zhou Y, Giscombe R, Huang D, Lefvert AK. Novel genetic association of Wegener's granulomatosis with the interleukin 10 gene. J Rheumatol. 2002;29(2):317–20.
62. Wieczorek S, Hellmich B, Arning L, Moosig F, Lamprecht P, Gross WL, et al. Functionally relevant variations of the interleukin-10 gene associated with antineutrophil cytoplasmic antibody-negative Churg-Strauss syndrome, but not with Wegener's granulomatosis. Arthritis Rheum. 2008;58(6):1839–48. doi:10.1002/art.23496.
63. Pravica V, Perrey C, Stevens A, Lee JH, Hutchinson IV. A single nucleotide polymorphism in the first intron of the human IFN-

gamma gene: absolute correlation with a polymorphic CA microsatellite marker of high IFN-gamma production. Hum Immunol. 2000;61(9):863–6.
64. Goldstein JD, Perol L, Zaragoza B, Baeyens A, Marodon G, Piaggio E. Role of cytokines in thymus- versus peripherally derived-regulatory T cell differentiation and function. Front Immunol. 2013;4:155. doi:10.3389/fimmu.2013.00155.
65. Boyman O, Sprent J. The role of interleukin-2 during homeostasis and activation of the immune system. Nat Rev Immunol. 2012;12(3):180–90. doi:10.1038/nri3156.
66. Carr EJ, Clatworthy MR, Lowe CE, Todd JA, Wong A, Vyse TJ, et al. Contrasting genetic association of IL2RA with SLE and ANCA-associated vasculitis. BMC Med Genet. 2009;10:22. doi:10.1186/1471-2350-10-22.
67. Dixit VD, Schaffer EM, Pyle RS, Collins GD, Sakthivel SK, Palaniappan R, et al. Ghrelin inhibits leptin- and activation-induced proinflammatory cytokine expression by human monocytes and T cells. J Clin Invest. 2004;114(1):57–66. doi:10.1172/JCI21134.
68. Wieczorek S, Holle JU, Bremer JP, Wibisono D, Moosig F, Fricke H, et al. Contrasting association of a non-synonymous leptin receptor gene polymorphism with Wegener's granulomatosis and Churg-Strauss syndrome. Rheumatology (Oxford). 2010;49(5):907–14. doi:10.1093/rheumatology/kep420.
69. Delgado-Vega AM, Alarcon-Riquelme ME, Kozyrev SV. Genetic associations in type I interferon related pathways with autoimmunity. Arthritis Res Ther. 2010;12 Suppl 1:S2.
70. Wieczorek S, Holle JU, Muller S, Fricke H, Gross WL, Epplen JT. A functionally relevant IRF5 haplotype is associated with reduced risk to Wegener's granulomatosis. J Mol Med (Berl). 2010;88(4):413–21. doi:10.1007/s00109-009-0580-y.
71. Tse WY, Abadeh S, McTiernan A, Jefferis R, Savage CO, Adu D. No association between neutrophil FcgammaRIIa allelic polymorphism and anti-neutrophil cytoplasmic antibody (ANCA)-positive systemic vasculitis. Clin Exp Immunol. 1999;117(1):198–205.
72. Edberg JC, Wainstein E, Wu J, Csernok E, Sneller MC, Hoffman GS, et al. Analysis of FcgammaRII gene polymorphisms in Wegener's granulomatosis. Exp Clin Immunogenet. 1997;14(3):183–95.
73. Dijstelbloem HM, Scheepers RH, Oost WW, Stegeman CA, van der Pol WL, Sluiter WJ, et al. Fcgamma receptor polymorphisms in Wegener's granulomatosis: risk factors for disease relapse. Arthritis Rheum. 1999;42(9):1823–7. doi:10.1002/1529-0131(199909)42:9<1823::AID-ANR5>3.0.CO;2-X.
74. Ramsland PA, Farrugia W, Bradford TM, Sardjono CT, Esparon S, Trist HM, et al. Structural basis for Fc gammaRIIa recognition of human IgG and formation of inflammatory signaling complexes. J Immunol. 2011;187(6):3208–17. doi:10.4049/jimmunol.1101467.
75. Wu J, Edberg JC, Redecha PB, Bansal V, Guyre PM, Coleman K, et al. A novel polymorphism of FcgammaRIIIa (CD16) alters receptor function and predisposes to autoimmune disease. J Clin Invest. 1997;100(5):1059–70. doi:10.1172/JCI119616.
76. Bredius RG, de Vries CE, Troelstra A, van Alphen L, Weening RS, van de Winkel JG, et al. Phagocytosis of Staphylococcus aureus and Haemophilus influenzae type B opsonized with polyclonal human IgG1 and IgG2 antibodies. Functional hFc gamma RIIa polymorphism to IgG2. J Immunol. 1993;151(3):1463–72.
77. Salmon JE, Edberg JC, Kimberly RP. Fc gamma receptor III on human neutrophils. Allelic variants have functionally distinct capacities. J Clin Invest. 1990;85(4):1287–95. doi:10.1172/JCI114566.
78. Tse WY, Abadeh S, Jefferis R, Savage CO, Adu D. Neutrophil FcgammaRIIIb allelic polymorphism in anti-neutrophil cytoplasmic antibody (ANCA)-positive systemic vasculitis. Clin Exp Immunol. 2000;119(3):574–7.
79. Kelley JM, Monach PA, Ji C, Zhou Y, Wu J, Tanaka S, et al. IgA and IgG antineutrophil cytoplasmic antibody engagement of Fc receptor genetic variants influences granulomatosis with polyangiitis. Proc Natl Acad Sci U S A. 2011;108(51):20736–41. doi:10.1073/pnas.1109227109.
80. Wu J, Ji C, Xie F, Langefeld CD, Qian K, Gibson AW, et al. FcalphaRI (CD89) alleles determine the proinflammatory potential of serum IgA. J Immunol. 2007;178(6):3973–82.
81. Pasquier B, Launay P, Kanamaru Y, Moura IC, Pfirsch S, Ruffie C, et al. Identification of FcalphaRI as an inhibitory receptor that controls inflammation: dual role of FcRgamma ITAM. Immunity. 2005;22(1):31–42. doi:10.1016/j.immuni.2004.11.017.
82. Tan SM. The leucocyte beta2 (CD18) integrins: the structure, functional regulation and signalling properties. Biosci Rep. 2012;32(3):241–69. doi:10.1042/BSR20110101.
83. Gencik M, Meller S, Borgmann S, Sitter T, Menezes Saecker AM, Fricke H, et al. The association of CD18 alleles with anti-myeloperoxidase subtypes of ANCA-associated systemic vasculitides. Clin Immunol. 2000;94(1):9–12. doi:10.1006/clim.1999.4811.
84. Meller S, Jagiello P, Borgmann S, Fricke H, Epplen JT, Gencik M. Novel SNPs in the CD18 gene validate the association with MPO-ANCA+ vasculitis. Genes Immun. 2001;2(5):269–72. doi:10.1038/sj.gene.6363781.
85. Campbell KS, Purdy AK. Structure/function of human killer cell immunoglobulin-like receptors: lessons from polymorphisms, evolution, crystal structures and mutations. Immunology. 2011;132(3):315–25. doi:10.1111/j.1365-2567.2010.03398.x.
86. Miyashita R, Tsuchiya N, Yabe T, Kobayashi S, Hashimoto H, Ozaki S, et al. Association of killer cell immunoglobulin-like receptor genotypes with microscopic polyangiitis. Arthritis Rheum. 2006;54(3):992–7. doi:10.1002/art.21653.
87. Anderson KJ, Allen RL. Regulation of T-cell immunity by leucocyte immunoglobulin-like receptors: innate immune receptors for self on antigen-presenting cells. Immunology. 2009;127(1):8–17. doi:10.1111/j.1365-2567.2009.03097.x.
88. Mamegano K, Kuroki K, Miyashita R, Kusaoi M, Kobayashi S, Matsuta K, et al. Association of LILRA2 (ILT1, LIR7) splice site polymorphism with systemic lupus erythematosus and microscopic polyangiitis. Genes Immun. 2008;9(3):214–23. doi:10.1038/gene.2008.5.
89. Persson U, Gullstrand B, Pettersson A, Sturfelt G, Truedsson L, Segelmark M. A candidate gene approach to ANCA-associated vasculitis reveals links to the C3 and CTLA-4 genes but not to the IL1-Ra and Fcgamma-RIIa genes. Kidney Blood Press Res. 2013;37(6):641–8. doi:10.1159/000355744.
90. Persson U, Truedsson L, Westman KW, Segelmark M. C3 and C4 allotypes in anti-neutrophil cytoplasmic autoantibody (ANCA)-positive vasculitis. Clin Exp Immunol. 1999;116(2):379–82.
91. Selsted ME, Ouellette AJ. Mammalian defensins in the antimicrobial immune response. Nat Immunol. 2005;6(6):551–7. doi:10.1038/ni1206.
92. Vordenbaumen S, Timm D, Bleck E, Richter J, Fischer-Betz R, Chehab G, et al. Altered serum levels of human neutrophil peptides (HNP) and human beta-defensin 2 (hBD2) in Wegener's granulomatosis. Rheumatol Int. 2011;31(9):1251–4. doi:10.1007/s00296-010-1702-0.
93. Groth M, Wiegand C, Szafranski K, Huse K, Kramer M, Rosenstiel P, et al. Both copy number and sequence variations affect expression of human DEFB4. Genes Immun. 2010;11(6):458–66. doi:10.1038/gene.2010.19.
94. Zhou XJ, Cheng FJ, Lv JC, Luo H, Yu F, Chen M, et al. Higher DEFB4 genomic copy number in SLE and ANCA-associated small vasculitis. Rheumatology (Oxford). 2012;51(6):992–5. doi:10.1093/rheumatology/ker419.