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Full Review

Genetic aspects of anti-neutrophil cytoplasmic antibody-associated vasculitis

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ABSTRACT

The genetics of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a complex area of investigation because of the low frequency of AAVs, the rarity of familial cases and the complexity of disease phenotypes. However, recent studies have been able to gather significant numbers of patients, and multicentre collaborative efforts have allowed the performance of two genome-wide association studies (GWASs). Genetic association studies based on candidate gene approaches and the two GWASs have greatly contributed to our current understanding of the genetic basis of AAV. The central role of autoimmunity has been confirmed by the significant association with HLA polymorphisms; interestingly, the three main AAV subtypes are associated with distinct HLA variants, i.e. granulomatosis with polyangiitis (Wegener's GPA) with *HLA-DP1*, microscopic polyangiitis with *HLA-DQ* and eosinophilic GPA (Churg-Strauss) with *HLA-DRB4*. GWASs also revealed that polymorphic variants of genes encoding proteinase 3 (PR3), the predominant antigenic target of ANCA in GPA, and its main inhibitor, alpha-1 antitrypsin, are highly associated with GPA and, even more significantly, with PR3-ANCA positivity (regardless of the clinical diagnosis); this emphasizes the central pathogenic role of PR3 and humoral autoimmunity in PR3-ANCA positive vasculitis. Finally, candidate gene approach studies have shown associations with other variants involved in autoimmunity, such as those belonging to the *CTLA-4* and *PTPN22* genes, although these findings warrant replication in larger studies. Additional studies are underway to better characterize disease associations within the AAV spectrum, which could provide new pathogenetic clues and possibly new treatment targets.

Keywords: ANCA, HLA, PTPN22, vasculitis

INTRODUCTION

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) refers to a group of small-vessel vasculitis, including granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis), microscopic polyangiitis (MPA) and eosinophilic GPA (EGPA, formerly Churg-Strauss syndrome) [1]. GPA and MPA are characterized by an extensive overlap in terms of clinical manifestations, mainly due to the possible vasculitic involvement of virtually all organ systems; however, the most frequent localizations are lung and kidney with pulmonary haemorrhage and rapidly progressive glomerulonephritis being the most severe manifestations [1]. Granulomatous involvement of the ear, nose and throat (ENT) system and of the lung is a frequent clinical feature of GPA and may represent the only localization in subgroups of patients [1]. Because of the frequent clinical overlap, GPA and MPA have been historically considered different ends of the same disease spectrum and therefore included together in clinical trials [2]. ANCA positivity is a feature of ~90% of GPA and MPA patients; ANCA is usually tested using indirect immunofluorescence, where two main patterns are observed, cytoplasmic (C-ANCA) and perinuclear (P-ANCA), and then confirmed using ELISA, which in most cases shows reactivity against proteinase 3 (PR3) or myeloperoxidase (MPO). GPA is usually associated with C-ANCA, directed against PR3, whereas MPA with P-ANCA, directed against MPO [3]; however, a significant overlap does exist with regard to the ANCA status; therefore although ANCA are often used to

confirm the diagnosis of AAV, ANCA specificity towards PR3 or MPO cannot be used to identify GPA versus MPA [4]. In EGPA, the main disease characteristics are asthma, peripheral eosinophilia, ENT involvement and eosinophil-rich lung infiltrates; vasculitic manifestations (e.g. glomerulonephritis, peripheral neuropathy and purpura) are less prevalent than in GPA and MPA and they appear to be more frequent in the 40% of EGPA patients that are ANCA-positive [3, 5].

Several candidate gene approach studies have been performed over the years; however, the understanding in the field of AAV genetics has dramatically increased after the publication of two genome-wide association studies (GWASs). The philosophy behind the GWAS is the interrogation of a high number of single-nucleotide polymorphisms (SNPs) that cover a big proportion of the human genome. This approach may be very informative; however, to avoid spurious associations, a very stringent P-value is required forcing a multicentre approach with big cohorts of patients. Two GWASs have been performed in AAV: the first conducted by the European Vasculitis Genetic Consortium (EVGC; 2687 cases of GPA and MPA, as well as 6858 controls) [6] and the second by the US Vasculitis Clinical Research Consortium (VCRC; 987 GPA cases and 2731 controls) [7].

In this review, we will discuss the main genetic associations that have emerged in AAV, and what they have added to our understanding of vasculitis. Tables 1 and 2 summarize the main genetic associations in AAV derived from non-GWAS and GWAS, respectively.

FULL REVIEW

GENETIC ASSOCIATIONS WITH AAVS

HLA region

The role of the HLA region in autoimmunity is central. Several associations with different *HLA* SNPs have been shown, for instance, in rheumatoid arthritis and type 1 diabetes [24, 25]. When acting as risk factors, *HLA* SNPs may promote positive selection of autoreactive T cells or prevent their negative selection [26].

The strongest evidence of HLA association in AAV is with the *HLA-DPB1*. This association has been initially described in a cohort of 150 German GPA patients ($P = 1.51 \times 10^{-10}$, OR 3.91) [27] and subsequently confirmed in an independent group of 108 German GPA patients [28]; in a further analysis of the combined cohort, the association remained significant only in the ANCA-positive patients ($P = 1.26 \times 10^{-22}$). This finding was then confirmed by the results of both GWASs: a strong association of an SNP in the *HLA-DPB1* area (OR 3.67, $P = 1.5 \times 10^{-71}$) resulted from the EVGC GWAS [6] as well as from the VCRC GWAS (OR 0.24, $P = 1.91 \times 10^{-50}$) [7]. The different directions of the OR observed between the two studies may be related to the different SNPs interrogated, the frequencies of each SNP minor allele in patients and controls or the modality of data analysis; nevertheless, both studies indicate a highly significant association between AAV and variations within *HLA-DPB1*.

Interestingly, a sub-analysis of the EVGC GWAS also showed that this association was stronger in the PR3-ANCA-positive subgroup ($P = 6.2 \times 10^{-89}$), independently of the clinical diagnosis, while this was not confirmed in the MPO-ANCA-positive subgroup. In the latter, a further analysis revealed an association with an SNP in the *HLA-DQ* region ($P = 2.1 \times 10^{-08}$), which had probably been masked by the small number of MPO-ANCA-positive patients in the primary analysis. This finding was further confirmed in an independent cohort of Italian cases [6].

Other associations have been described in small or not replicated studies. In a Dutch cohort of 241 patients with GPA, a lower proportion of *HLA-DR13(6)* and *HLA-DR1* and an increased proportion of *HLA-DR4* were found compared with controls [29]; no replication of these data has been published so far. In two small cohorts of 32 African-American and 74 Caucasian patients, an association with *HLA-DRB1* was documented in PR3-ANCA-positive patients, but not in the MPO-positive ones [30]; interestingly, an association with a variation in the same HLA locus has been documented in a cohort of 152 Chinese patients with GPA and MPA [31]. Relatively small studies documented an association of GPA with *HLA-B50*, *HLA-DR1*, *HLA-DR9*, *HLA-DQw7* and *HLA-DR3* [32–34].

In MPA, few data are available; the most interesting report is from a group of 50 MPO-ANCA-positive Japanese patients, where an association with the *HLA-DRB1*0901* ($P = 0.033$) and *HLA-DQB1*0303* ($P = 0.022$) was documented. The small numbers and the high linkage disequilibrium between the two alleles (D' 0.95, $r^2 = 0.82$) did not allow the identification of the independent variant [11]. Quite interesting is the confirmation of the association of the *HLA-DQB1* with anti-MPO-positive patients emerged from the EVGC GWAS in a third cohort of different ethnicity. A study performed with 107 Chinese patients with MPA showed another potential association with *HLA-DRB1*1101* ($P = 0.023$) [31]; further studies will need to clarify if this is a genuine association or only expression of a non-random inheritance of this allele as part of a haplotype with a specific *HLA-DQB1*.

In EGPA, the most robust association that has emerged so far is that with *HLA-DRB4*; this has been shown in an Italian study with 48 patients (OR 2.49, $P = 0.000232$) [13] and has been replicated in an independent study of 102 German EGPA subjects (OR 1.87, $P = 0.0002$) [12].

In summary, the findings of an association for all AAVs with SNPs in the HLA region have confirmed the existence of a likely autoimmune component in their pathogenesis. Different loci in the HLA region seem to be involved in the different AAV subtypes, thus suggesting that they have a distinct genetic background. Moreover, the results of the EVGC GWAS seem to support a genetic distinction between AAV forms, which is more closely related to ANCA specificity rather than to the clinical diagnosis.

PRTN3—SERPINA1 genes

The presence of autoantibodies against the neutrophil serum protease PR3 suggested its potential role in the development of GPA. PR3 may be stored in the neutrophil azurophilic granules as well as exposed on the neutrophil cell membrane [35]. Interestingly, PR3 surface expression is bimodal, with the antigen present on the surface of a proportion of the

Table 1. Main genetic associations with AAV excluding those deriving from GWASs

Gene	Variation	Population	Cases	Controls	OR	P-value	Author, year (reference)
CD226	*rs763361*	German	642 GPA	1226	1.02	0.016	Wieczorek, 2009 [8]
CTLA4	*rs3087243*	British	641 (GPA, MPA and EGPA)	9.115	1.19	6.4×10^{-3}	Carr, 2009 [9]
GHSR	*Haplotype*	German	460 GPA	878	1.30	0.026	Wieczorek, 2010 [10]
*HLA-DQB1*0303*		Japanese	50 MPA	77	2.35	0.017	Tsuchiya, 2006 [11]
*HLA-DRB1*04*		German	102 EGPA	341	0.10	0.0028	Wieczorek, 2008 [12]
*HLA-DRB1*07*		Italian	48 EGPA	350	2.42	0.0042	Vaglio, 2007 [13]
*HLA-DRB1*07*		German	102 EGPA	341	1.57	0.046	Wieczorek, 2008 [12]
*HLA-DRB1*0901-DQB1*0303*		Japanese	50 MPA	77	2.44	0.0037	Tsuchiya, 2006 [11]
*HLA-DRB1*13*		German	102 EGPA	341	0.50	0.019	Wieczorek, 2008 [12]
HLA-DRB3		Italian	48 EGPA	350	0.54	0.028	Vaglio, 2007 [13]
HLA-DRB3		German	102 EGPA	341	0.04	0.004	Wieczorek, 2008 [12]
HLA-DRB4		Italian	48 EGPA	350	2.49	0.00023	Vaglio, 2007 [13]
HLA-DRB4		German	102 EGPA	341	0.10	0.0002	Wieczorek, 2008 [12]
IL-10	*Haplotype*	German	103 EGPA	507	2.16	0.0003	Wieczorek, 2008 [14]
IL2RA	*rs41295061*	British	675 (GPA, MPA and EGPA)	8.936	0.05	0.012	Carr, 2009 [15]
IRF5	*Haplotype*	German	664 GPA	952	0.05	0.0012	Wieczorek, 2010 [16]
KIR2	*DS3*	Japanese	43 MPA	239	0.24	0.038	Miyashita, 2006 [17]
LEPR	*Lys656Asn*	German	460 GPA	878	0.05	0.0013	Wieczorek, 2010 [10]
LEPR	*Lys656Asn*	German	196 EGPA	878	1.41	0.0067	Wieczorek, 2010 [10]
LILRA2	*rs2241524 AA genotype*	Japanese	50 MPA	284	2.52	0.049	Mamegano, 2008 [18]
PTPN22	*rs2476601*	German	199 GPA	399	1.08	0.002	Jagiello, 2005 [19]
PTPN22	*rs2476601*	Italian	143 GPA, 102 MPA and 99 EGPA	945	1.91 GPA; 2.31 ANCA + GPA	0.005 GPA; 0.00012 ANCA + GPA	Martorana, 2012 [20]
PTPN22	*rs2476601*	British	641 (GPA, MPA and EGPA)	9.115	1.04	0.000140	Carr, 2009 [9]
TLR9	*3-SNP haplotype*	German, Dutch, British	646 GPA, 164 EGPA and 53 MPA German; 273 GPA, 53 EGPA and 100 MPA Dutch and British AAV cases	1898	0.60	0.000044	Husmann, 2013 [21]
FCGR3B CNVs	*High CNVs*	British	556 (GPA, MPA and EGPA)	286	/	1×10^{-8}	Willcocks, 2008 [22]
FCGR3B CNVs	*Low CNVs*	British	76 MPA	190	/	0.0003	Fanciulli, 2007 [23]

All genetic association studies on MPA and EGPA were reported, whereas for GPA we only included studies with a sample size of >400 patients.

Table 2. Main genetic associations with AAV deriving from the two GWASs

Gene	Variation	Population	Cases	Controls	OR	P-value
GWAS performed by the EVGC (Lyons *et al.* 2012) [6]						
HLA-DP	rs3117242	European	2267 GPA and MPA	6858	3.67	1.5×10^{-71}
HLA-DQ	rs5000634	European	2267 GPA and MPA	6858	0.80	2.9×10^{-9}
COL11A2	rs3130233	European	2267 GPA and MPA	6858	1.51	7.8×10^{-15}
COL11A2	rs3117016	European	2267 GPA and MPA	6858	1.83	6.4×10^{-24}
SERPINA1	rs7151526	European	2267 GPA and MPA	6858	0.59	2.4×10^{-9}
HLA-DP	rs3117242	European	1683 GPA	6858	5.39	3.1×10^{-85}
HLA-DQ	rs5000634	European	1683 GPA	6858	0.83	2.2×10^{-6}
ARHGAP18	rs1705767	European	1683 GPA	6858	0.78	3.3×10^{-7}
SERPINA1	rs7151526	European	1683 GPA	6858	0.54	4.4×10^{-10}
PRTN3	rs62132295	European	1683 GPA	6858	0.78	2.6×10^{-5}
MOSPD2	rs6628825	European	1683 GPA	6858	0.80	2.6×10^{-6}
HLA-DP	rs3117242	European	489 MPA	6858	1.60	1.3×10^{-3}
HLA-DQ	rs5000634	European	489 MPA	6858	0.67	1.4×10^{-5}
ARHGAP18	rs1705767	European	489 MPA	6858	0.84	1.8×10^{-2}
SERPINA1	rs7151526	European	489 MPA	6858	0.76	1.7×10^{-1}
PRTN3	rs62132295	European	489 MPA	6858	0.99	9.3×10^{-1}
MOSPD2	rs6628825	European	489 MPA	6858	0.79	2.2×10^{-1}
HLA-DP	rs3117242	European	1521 PR3+	6858	7.03	6.2×10^{-89}
HLA-DQ	rs5000634	European	1521 PR3+	6858	0.86	3.3×10^{-5}
ARHGAP18	rs1705767	European	1521 PR3+	6858	0.73	5.2×10^{-8}
SERPINA1	rs7151526	European	1521 PR3+	6858	0.53	5.6×10^{-12}
PRTN3	rs62132295	European	1521 PR3+	6858	0.73	2.6×10^{-7}
MOSPD2	rs6628825	European	1521 PR3+	6858	0.77	6.1×10^{-7}
HLA-DP	rs3117242	European	556 MPO+	6858	1.55	3.2×10^{-2}
HLA-DQ	rs5000634	European	556 MPO+	6858	0.65	2.1×10^{-8}
ARHGAP18	rs1705767	European	556 MPO+	6858	0.87	1.0×10^{-2}
SERPINA1	rs7151526	European	556 MPO+	6858	0.84	2.8×10^{-1}
PRTN3	rs62132295	European	556 MPO+	6858	1.10	2.2×10^{-1}
MOSPD2	rs6628825	European	556 MPO+	6858	0.86	6.3×10^{-1}
GWAS performed by the VCRC (Xie *et al.* 2013) [7]						
HLA-DPB1	rs9277554	European descent	750 GPA	1820	0.24	1.92×10^{-50}
HLA-DPA1	rs9277341	European descent	750 GPA	1820	0.33	2.18×10^{-39}
WSCD1	rs7503953	European descent	750 GPA	1820	1.50	1.93×10^{-7}
COBL	rs1949829	European descent	750 GPA	1820	1.78	4.19×10^{-7}
CCDC86	rs595018	European descent	750 GPA	1820	1.46	1.60×10^{-7}
DCTD	rs4862110	European descent	750 GPA	1820	1.44	2.14×10^{-6}
SEMA6A	rs26595	European descent	750 GPA	1820	0.74	2.09×10^{-8}
HLA-DPB1	rs9277554	European descent	578 C-ANCA+	1820	0.16	4.7×10^{-57}
HLA-DPA1	rs9277341	European descent	578 C-ANCA+	1820	0.27	2.30×10^{-42}

neutrophils (defined as mPR3+), but not on all of them (mPR3−). The membrane-bound form is the one able to interact directly with the ANCA [36], precipitating neutrophil activation and their endothelial adhesion. Neutrophil priming is a key process in order to increase surface expression of PR3 in the subgroup of mPR3+ neutrophils [37], but the proportion of mPR3+ and mPR3− cells remains stable over time. A phenotype with a high proportion of mPR3+ neutrophils is more frequent in patients with AAV when compared with controls (85 versus 55%) [38]. These observations, together with the demonstration of the high stability over time of the ratio of mPR3+/mPR3− neutrophils in controls ($r = 0.94$) and the high concordance of this proportion in monozygotic twins ($r = 0.99$) but not in dizygotic twins ($r = 0.06$) [39], have suggested that the cell surface expression of PR3 is genetically determined.

A non-replicated study that screened the coding and promoter sequences of *PRTN3* (the gene encoding PR3) in 79 GPA patients and 129 controls demonstrated an association between the disease and an SNP of the promoter region (A564G) affecting a transcription factor-binding site (OR 4.2, $P < 0.00001$) [40]. The association of the *PRTN3* gene SNP rs62132295 has also been interrogated in the EVGC GWAS, where a subgroup analysis revealed that it was significantly associated with GPA (OR 0.78, $P = 2.6 \times 10^{-5}$). As observed for the above-mentioned HLA association, the strength of the *PRTN3* SNP signal increased in the PR3-ANCA-positive subgroup, independently of the clinical diagnosis (OR 0.73, $P = 2.6 \times 10^{-7}$). No association with *PRTN3* emerged in the MPO-ANCA-positive patients [6], which indicates a role for *PRTN3* only in the pathogenesis of anti-PR3-positive AAV.

PR3 is also central in mediating direct tissue damage after neutrophil activation has occurred and the enzyme is released from the cell. Alpha-1 antitrypsin, encoded by the gene *SERPINA1* on chromosome 14, represents the major inhibitor of PR3 activity. Two alpha-1 antitrypsin alleles, Z and S, have been described as associated with low enzymatic activity; studies in small cohorts suggested an association of both of these alleles with GPA [41–43]. The mechanism behind this was, and still is, unclear: it has been proposed that an

enhanced reactivity of the immune system against an insufficiently cleared PR3 might play a central role [44]; however, other evidence draws attention to the insufficient inhibition of the PR3 protease activity in peripheral tissues as responsible for more severe damage rather than a role as a proper risk factor for the development of the disease [45]. The largest study performed in the pre-GWAS era screened 433 Caucasian patients with GPA and 421 controls, and compared the frequency of the Z and S alleles, showing in 10 patients carrying the SS, ZZ or SZ genotypes an OR for the development of GPA of 14.58 ($P = 0.002$); the small number of cases was responsible for a broad confidence interval, suggesting caution in the interpretation of these findings [46]. In this context, significant results came from the results of the EVGC GWAS, which showed the association of a SNP in the *SERPINA1* gene with AAVs (OR 0.59, $P = 2.4 \times 10^{-9}$). As per *PRTN3* findings, this association was stronger in GPA patients (OR 0.54, $P = 4.4 \times 10^{-10}$) and even more significant in the PR3-ANCA-positive subgroup, independently of the clinical diagnosis (OR 0.53, $P = 5.6 \times 10^{-12}$) [6]. The tag SNP identified in the GWAS is in linkage disequilibrium with the Z allele, confirming that this can be a risk factor for the development of the disease.

Fine mapping of the *PRTN3* and *SERPINA1* area is required for a better understanding of the genetic variations responsible for the risk of developing GPA and for further improvement in the pathogenic understanding.

Other replicated associations—*PTPN22* and *CTLA4*

The interaction between ANCA and neutrophils is a central pathogenetic event in AAV. However, this represents only one component of a more complex picture. The role of B cells is also pivotal, as shown by the effectiveness of the anti-CD20 agent rituximab as a therapeutic option [47]. ANCA production is one of several B cell functions in AAV; these cells also provide T-cell support acting as antigen-presenting cells and are able to produce pro-inflammatory cytokines [48]. T-cells are also heavily involved as proven by their general hyperactivity in AAV and by the prominent role of the $CD4^+$ T effector memory cells in causing endothelial damage [49]. It is therefore not surprising that SNPs within genes encoding B- and T-cell-specific proteins have been identified as potential risk factors for AAV.

The gene *PTPN22* encodes the lymphoid tyrosine phosphatase (Lyp). Abnormal regulatory CD4 T-cell (T_{reg}) function, increased humoral activity [50] and enhanced neutrophil functions [51] have been described as features of the 620W *PTPN22* variant; its role in AAV seemed indeed reasonable and provided the basis for the three main *PTPN22* genetic association studies performed so far. The first, which included a German cohort of 199 GPA patients and 399 controls, showed an association of this variant with the disease (OR 1.75, $P = 0.002$); the association was even more significant in the ANCA-positive subgroup (OR 2.01, $P = 0.0002$) [19]. This result has been subsequently replicated in two independent cohorts of 641 British (OR 1.40, $P = 1.4 \times 10^{-4}$) [9] and 344 Italian AAV patients [20]. Interestingly, the latter study showed that the association was restricted to the 143 GPA patients (OR 1.91, $P = 0.005$), but that the frequency of the 620W *PTPN22* variant was comparable between the controls ($n = 945$) and the 102 MPA ($P = 0.1072$) or the 99 EGPA patients ($P = 0.1508$). The GPA population was PR3-ANCA-positive in nearly 80% of the cases, whereas the MPA subgroup was MPO-ANCA-positive in ~90%.

CTLA4 is an inhibitory glycoprotein expressed on activated T cells, which competes with the co-stimulatory molecule CD28 for the binding of CD80 or CD86 on the antigen-presenting cells [52]. The monoclonal antibody abatacept, whose efficacy in controlling disease activity was demonstrated in a recent trial in GPA patients with non-severe manifestations [53], contains the binding domain of CTLA4, thus reducing the interaction CD28–CD80/CD86 and therefore T-cell stimulation. A role for genetic variants in the *CTLA4* gene or other genes involved in its pathway may therefore be of interest in AAV [54, 55]. The more robust finding so far involves the SNP rs3087243, interrogated in two large cohorts of British patients; the first study found an association in 222 AAV patients ($P = 0.0001$) [56], and the second confirmed it in an independent cohort of 641 AAV patients ($P = 6.4 \times 10^{-3}$) [9].

Other associations

The VCRC GWAS in AAV identified a potential association of GPA with the gene *SEMA6A* ($P = 2.09 \times 10^{-8}$) encoding the protein semaphorin 6A [7]. The function of the proteins belonging to this family is unclear, but it has been proposed that they may be involved in immune regulation [57]. The association between the rs26595 SNP of the *SEM6A* gene and GPA was recently investigated also in a different cohort of Northern European patients, including 879 GPA, 150 MPA and 191 EGPA [58]. No statistically significant difference in allele frequencies was observed in this group, suggesting the necessity of further studies to better clarify the role of this region in AAV.

IL10 is a cytokine with anti-inflammatory activity. A study performed on 32 patients and replicated on 125 additional cases proposed an association of its (−1082) SNP in GPA [59, 60]; interestingly, the latter report showed a signal for the same SNP in 36 MPA patients ($P < 0.00001$) [60]. A subsequent, larger study performed on 403 German GPA patients did not confirm this finding, but showed an association with a specific *IL10* haplotype ($P = 0.0003$) in 75 patients with ANCA-negative EGPA [14].

The high-affinity IL2 receptor, encoded by the gene *IL2RA*, is expressed not only on activated T cells, but also on activated B cells, NK cells and monocytes [61]. A normal IL2–IL2RA pathway is central for a physiological function of the immune system and for the development of a normal T_{reg} repertoire [62]. A weak association ($P = 0.0122$) has been documented in 670 British patients with AAV for the SNP rs41295061 [15]; replication in an independent cohort is required before considering this SNP as a potential risk factor.

CD226 is an adhesion molecule belonging to the immunoglobulin superfamily. *In vitro* stimulation of CD226 potentiates NK-mediated cytotoxicity [63] and provides a positive co-stimulatory signal for T-cell proliferation. An association between *CD226* and GPA was documented in two distinct cohorts of 520 and 122 German GPA patients (respectively,

OR 1.2; P = 0.020 and OR 1.37, P = 0.020); however, further replication failed in 105 British GPA patients [8]. A further independent replication study on a cohort of 641 British AAV cases found no association (P = 0.21) [9]. Interestingly, the two populations were of similar size and showed similar frequency of the SNP analysed (0.47 versus 0.50), suggesting as unlikely a different effect of the SNP in these populations.

Fc gamma receptors (FCGRs) are a group of proteins expressed on the surface of different cell types with different affinity for the Fc portion of different IgG subclasses [64], suggesting a reasonable potential role for FCGRs in AAV. However, the genes encoding these receptors are located in a highly variable area (locus 1q23.3), whose genotyping has proven challenging due to high variability in terms of SNPs and copy number variations (CNVs) [64]. A Dutch study identified a SNP of *FCGR2A* and *FCGR3A* as potential risk factors for GPA in a cohort of 91 patients [65], but the finding was not confirmed, at least for the *FCGR2A* SNP, in a cohort of 107 British patients [66]. CNVs of *FCGR3B* have been investigated in two cohorts of patients with contrasting results: an association was documented using qPCR in 80 UK patients with GPA and replicated in 77 French and 76 MPA patients [23]. However, this was not confirmed in 567 AAV patients when a different approach was used (paralogue ratio test) [67]. The availability of new genotyping techniques will shed light on the potential association of this complex area with AAV.

Interferon regulatory factor 5 (IRF5) is a transcriptional factor able to induce transcription of IFN-alpha mRNA [68]. A large association study on 644 GPA failed to identify an association between *IRF5* SNPs and disease; however, a potential protective haplotype was identified (P = 0.0012) [16]. Interestingly, one of these SNPs (rs10954213) has been recently identified as in association with MPO-ANCA-positive AAV in 177 Japanese patients (OR 1.27, P = 0.023) [69].

A well-established role in the development of AAVs is played by infection. Any chronic infection, particularly nasal carriage of *Staphylococcus aureus*, is considered a potential trigger of the disease [70]. Toll-like receptors (TLRs) are a group of proteins able to recognize microbiological structures and activate immune responses. SNPs of *TLR9* have been shown to be associated with GPA, MPA and PR3-associated AAV in a cohort of 863 AAV patients; however, the findings were not replicated in a small independent cohort. Interestingly, MPO-ANCA-positive disease was associated with the contrary allele compared with the PR3-ANCA subset, leading to a significant difference between the two groups for the SNP rs352140 (P = 0.000016) [21]. Defensins are cationic proteins characterized by intrinsic antimicrobial activity [71]; a weak association between CNVs of the defensin gene *DEFB4* and GPA has been documented in a small cohort of Chinese patients [72].

Few further associations have been documented so far. In a cohort of 460 GPA patients, an association with a leptin SNP was found and replicated in 226 patients (OR 0.72 P = 0.0013); interestingly, genotyping of the same SNP in 196 EGPA patients confirmed the association but with contrasting allele distribution (OR 1.41, P = 0.0067) [10]. A small Japanese study identified a weak association between a leucocyte immunoglobulin-like receptor (*LILRA2*) and MPA (P = 0.049) [18]; finally, genetic variants of genes encoding complement proteins *C3F* and *C4A3* have been associated with AAV in 67 patients [73].

GENETIC FINDINGS AND DISEASE PHENOTYPES

Genetic studies have been fundamental for the understanding of AAV so far. They have confirmed that the single disease entities grouped under the umbrella of AAV may reasonably be considered distinct diseases also because of their different genetic background. Moreover, it is now quite clear how GPA and MPA may be more correctly re-defined according to the ANCA specificity (PR3 versus MPO) rather than on the basis of their clinical phenotype. This is not surprising since several clinical findings were already pointing towards that direction, such as the different prognosis associated with anti-PR3 or anti-MPO ANCA positivity [74] as well as the different cardiovascular risk between these groups and the higher proportion of extrarenal manifestation in anti-PR3-positive patients [75–81] (Table 3). These studies have also confirmed the central role of autoimmunity in AAV, as evidenced by the strong association with HLA and SNPs typical of other autoimmune diseases. More detailed are at the moment the evidences available for GPA—easier to study given its higher prevalence—where a crucial role has been shown also for the autoantigen PR3 and for its main inhibitor alpha-1 antitrypsin.

Although very informative, all these findings represent only the beginning of a new exciting and dynamic phase in this field.

Table 3. Major distinctive clinical features between PR3-ANCA and MPO AAV (irrespective of the clinical diagnosis)

Variable	PR3-ANCA	MPO-ANCA	Author, year (reference)
Mean age at onset (years)	56–59	62–65	de Joode, 2013 [76]; Quintana, 2014 [77]
Male gender	66%	48%	de Joode, 2013 [76]
ENT involvement	77%	23%	de Joode, 2013 [76]
Eye involvement	40%	15%	Franssen, 1998 [78]
Kidney-limited disease	2%	31%	de Joode, 2013 [76]
Interstitial lung disease	0	7.2%[a]	Arulkumaran, 2011 [79]
Relapse (hazard ratio of relapse of PR3+ versus MPO+ patients)	1.89 (95% CI 1.33–2.69)		Lionaki, 2012 [80]
Relapse (relapse-free patients 5 years after diagnosis)	32%	60%	Lionaki, 2012 [80]
Cardiovascular risk (patients with ≥1 cardiovascular event over 5-year follow-up)	6.6%	19.2%	Suppiah, 2011 [81]

[a]This percentage was calculated out of the patients with MPA (14/194 MPA patients studied had interstitial lung disease); all patients with interstitial lung disease were MPO-ANCA-positive.

The next step will be to analyse larger GWASs or association studies in patients with anti-PR3 and anti-MPO AAV as separate entities in order to be more powered for the identification of further antibody-specific associations. The collection of larger cohorts or the metanalysis of data deriving from different existing cohorts will probably be of help also in identifying predisposing variants shared by the different ANCA subsets, which is quite expected given the significant clinical overlap between anti-PR3 and anti-MPO AAVs. The enrolment of patients in national and international registries characterized by long follow-up and detailed clinical data will make longitudinal studies possible for the identification of genetic predictors of disease severity and clinical outcome. A GWAS in EGPA is definitely warranted to allow an improvement in the understanding of the disease and only the cooperation of several centres will allow a sufficiently powered approach.

We should not forget that the identification of an association between a tag SNP and a disease could be flag of an association present somewhere in the identified area, but potentially related to other variants in linkage disequilibrium with the SNP analysed. Fine mapping approaches are therefore necessary for the identification of the real associations and this may, in the long term, allow for the development of more targeted therapeutic approaches.

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CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Jennette JC, Falk RJ, Andrassy K *et al.* Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum 1994; 37: 187–192
2. Jayne D, Rasmussen N, Andrassy K *et al.* A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. N Engl J Med 2003; 349: 36–44
3. Mahr A, Katsahian S, Varet H *et al.* Revisiting the classification of clinical phenotypes of anti-neutrophil cytoplasmic antibody-associated vasculitis: a cluster analysis. Ann Rheum Dis 2013; 72: 1003–1010
4. Watts R, Lane S, Hanslik T *et al.* Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. Ann Rheum Dis 2007; 66: 222–227
5. Sable-Fourtassou R, Cohen P, Mahr A *et al.* Antineutrophil cytoplasmic antibodies and the Churg-Strauss syndrome. Ann Intern Med 2005; 143: 632–638
6. Lyons PA, Rayner TF, Trivedi S *et al.* Genetically distinct subsets within ANCA-associated vasculitis. N Engl J Med 2012; 367: 214–223
7. Xie G, Roshandel D, Sherva R *et al.* Association of granulomatosis with polyangiitis (Wegener's) with HLA-DPB1*04 and SEMA6A gene variants: evidence from genome-wide analysis. Arthritis Rheum 2013; 65: 2457–2468
8. Wieczorek S, Hoffjan S, Chan A *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: 591–595
9. Carr EJ, Niederer HA, Williams J *et al.* Confirmation of the genetic association of CTLA4 and PTPN22 with ANCA-associated vasculitis. BMC Med Genet 2009; 10: 121
10. Wieczorek S, Holle JU, Bremer JP *et al.* Contrasting association of a non-synonymous leptin receptor gene polymorphism with Wegener's granulomatosis and Churg-Strauss syndrome. Rheumatology (Oxford) 2010; 49: 907–914
11. Tsuchiya N, Kobayashi S, Hashimoto H *et al.* Association of HLA-DRB1*0901-DQB1*0303 haplotype with microscopic polyangiitis in Japanese. Genes Immun 2006; 7: 81–84
12. Wieczorek S, Hellmich B, Gross WL *et al.* 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: 329–330
13. Vaglio A, Martorana D, Maggiore U *et al.* HLA-DRB4 as a genetic risk factor for Churg-Strauss syndrome. Arthritis Rheum 2007; 56: 3159–3166
14. Wieczorek S, Hellmich B, Arning L *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: 1839–1848
15. Carr EJ, Clatworthy MR, Lowe CE *et al.* Contrasting genetic association of IL2RA with SLE and ANCA-associated vasculitis. BMC Med Genet 2009; 10: 22
16. Wieczorek S, Holle JU, Muller S *et al.* A functionally relevant IRF5 haplotype is associated with reduced risk to Wegener's granulomatosis. J Mol Med (Berl) 2010; 88: 413–421
17. Miyashita R, Tsuchiya N, Yabe T *et al.* Association of killer cell immunoglobulin-like receptor genotypes with microscopic polyangiitis. Arthritis Rheum 2006; 54: 992–997
18. Mamegano K, Kuroki K, Miyashita R *et al.* Association of LILRA2 (ILT1, LIR7) splice site polymorphism with systemic lupus erythematosus and microscopic polyangiitis. Genes Immun 2008; 9: 214–223
19. Jagiello P, Aries P, Arning L *et al.* The PTPN22 620W allele is a risk factor for Wegener's granulomatosis. Arthritis Rheum 2005; 52: 4039–4043
20. Martorana D, Maritati F, Malerba G *et al.* PTPN22 R620W polymorphism in the ANCA-associated vasculitides. Rheumatology (Oxford) 2012; 51: 805–812
21. Husmann CA, Holle JU, Moosig F *et al.* Genetics of toll like receptor 9 in ANCA associated vasculitides. Ann Rheum Dis 2014; 73: 890–896
22. Willcocks LC, Lyons PA, Clatworthy MR *et al.* Copy number of FCGR3B, which is associated with systemic lupus erythematosus, correlates with protein expression and immune complex uptake. J Exp Med 2008; 205: 1573–1582
23. Fanciulli M, Norsworthy PJ, Petretto E *et al.* FCGR3B copy number variation is associated with susceptibility to systemic, but not organ-specific, autoimmunity. Nat Genet 2007; 39: 721–723
24. Raychaudhuri S, Sandor C, Stahl EA *et al.* Five amino acids in three HLA proteins explain most of the association between MHC and seropositive rheumatoid arthritis. Nat Genet 2012; 44: 291–296
25. Baschal EE, Aly TA, Babu SR *et al.* HLA-DPB1*0402 protects against type 1A diabetes autoimmunity in the highest risk DR3-DQB1*0201/DR4-DQB1*0302 DAISY population. Diabetes 2007; 56: 2405–2409
26. Taneja V, Behrens M, Basal E *et al.* Delineating the role of the HLA-DR4 'shared epitope' in susceptibility versus resistance to develop arthritis. J Immunol 2008; 181: 2869–2877
27. Jagiello P, Gencik M, Arning L *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: 468–477
28. Heckmann M, Holle JU, Arning L *et al.* The Wegener's granulomatosis quantitative trait locus on chromosome 6p21.3 as characterised by tagSNP genotyping. Ann Rheum Dis 2008; 67: 972–979
29. Stassen PM, Cohen-Tervaert JW, Lems SP *et al.* HLA-DR4, DR13(6) and the ancestral haplotype A1B8DR3 are associated with ANCA-associated vasculitis and Wegener's granulomatosis. Rheumatology (Oxford) 2009; 48: 622–625

30. Cao Y, Schmitz JL, Yang J *et al.* DRB1*15 allele is a risk factor for PR3-ANCA disease in African Americans. J Am Soc Nephrol 2011; 22: 1161–1167
31. Luo H, Chen M, Yang R *et al.* The association of HLA-DRB1 alleles with antineutrophil cytoplasmic antibody-associated systemic vasculitis in Chinese patients. Hum Immunol 2011; 72: 422–425
32. Cotch MF, Fauci AS, Hoffman GS. HLA typing in patients with Wegener granulomatosis. Ann Intern Med 1995; 122: 635
33. Papiha SS, Murty GE, Ad'Hia A *et al.* Association of Wegener's granulomatosis with HLA antigens and other genetic markers. Ann Rheum Dis 1992; 51: 246–248
34. Spencer SJ, Burns A, Gaskin G *et al.* HLA class II specificities in vasculitis with antibodies to neutrophil cytoplasmic antigens. Kidney Int 1992; 41: 1059–1063
35. Witko-Sarsat V, Cramer EM, Hieblot C *et al.* Presence of proteinase 3 in secretory vesicles: evidence of a novel, highly mobilizable intracellular pool distinct from azurophil granules. Blood 1999; 94: 2487–2496
36. Campbell EJ, Campbell MA, Owen CA. Bioactive proteinase 3 on the cell surface of human neutrophils: quantification, catalytic activity, and susceptibility to inhibition. J Immunol 2000; 165: 3366–3374
37. Yang JJ, Tuttle RH, Hogan SL *et al.* Target antigens for anti-neutrophil cytoplasmic autoantibodies (ANCA) are on the surface of primed and apoptotic but not unstimulated neutrophils. Clin Exp Immunol 2000; 121: 165–172
38. Witko-Sarsat V, Lesavre P, Lopez S *et al.* A large subset of neutrophils expressing membrane proteinase 3 is a risk factor for vasculitis and rheumatoid arthritis. J Am Soc Nephrol 1999; 10: 1224–1233
39. Schreiber A, Busjahn A, Luft FC *et al.* Membrane expression of proteinase 3 is genetically determined. J Am Soc Nephrol 2003; 14: 68–75
40. Gencik M, Meller S, Borgmann S *et al.* Proteinase 3 gene polymorphisms and Wegener's granulomatosis. Kidney Int 2000; 58: 2473–2477
41. Elzouki AN, Segelmark M, Wieslander J *et al.* Strong link between the alpha 1-antitrypsin PiZ allele and Wegener's granulomatosis. J Intern Med 1994; 236: 543–548
42. Baslund B, Szpirt W, Eriksson S *et al.* Complexes between proteinase 3, alpha 1-antitrypsin and proteinase 3 anti-neutrophil cytoplasm autoantibodies: a comparison between alpha 1-antitrypsin PiZ allele carriers and non-carriers with Wegener's granulomatosis. Eur J Clin Invest 1996; 26: 786–792
43. Borgmann S, Endisch G, Urban S *et al.* A linkage disequilibrium between genes at the serine protease inhibitor gene cluster on chromosome 14q32.1 is associated with Wegener's granulomatosis. Clin Immunol 2001; 98: 244–248
44. Stoller JK, Aboussouan LS. Alpha1-antitrypsin deficiency. Lancet 2005; 365: 2225–2236
45. Segelmark M, Elzouki AN, Wieslander J *et al.* The PiZ gene of alpha 1-antitrypsin as a determinant of outcome in PR3-ANCA-positive vasculitis. Kidney Int 1995; 48: 844–850
46. Mahr AD, Edberg JC, Stone JH *et al.* Alpha(1)-antitrypsin deficiency-related alleles Z and S and the risk of Wegener's granulomatosis. Arthritis Rheum 2010; 62: 3760–3767
47. Alberici F, Jayne DR. Impact of rituximab trials on the treatment of ANCA-associated vasculitis. Nephrol Dial Transplant 2014; 29: 1151–1159
48. Shlomchik MJ, Craft JE, Mamula MJ. From T to B and back again: positive feedback in systemic autoimmune disease. Nat Rev Immunol 2001; 1: 147–153
49. Abdulahad WH, De Souza AW, Kallenberg CG. L3. Are mononuclear cells predominant actors of endothelial damage in vasculitis? Presse Med 2013; 42(4 Pt 2): 499–503
50. Maine CJ, Hamilton-Williams EE, Cheung J *et al.* PTPN22 alters the development of regulatory T cells in the thymus. J Immunol 2012; 188: 5267–5275
51. Bayley R, Kite KA, McGettrick HM *et al.* The autoimmune-associated genetic variant PTPN22 R620W enhances neutrophil activation and function in patients with rheumatoid arthritis and healthy individuals. Ann Rheum Dis 2014; doi: 10.1136/annrheumdis-2013-204796
52. Noel PJ, Boise LH, Green JM *et al.* CD28 costimulation prevents cell death during primary T cell activation. J Immunol 1996; 157: 636–642
53. Langford CA, Monach PA, Specks U *et al.* An open-label trial of abatacept (CTLA4-IG) in non-severe relapsing granulomatosis with polyangiitis (Wegener's). Ann Rheum Dis 2014; 73: 1376–1379
54. Giscombe R, Wang X, Huang D *et al.* Coding sequence 1 and promoter single nucleotide polymorphisms in the CTLA-4 gene in Wegener's granulomatosis. J Rheumatol 2002; 29: 950–953
55. Slot MC, Sokolowska MG, Savelkouls KG *et al.* Immunoregulatory gene polymorphisms are associated with ANCA-related vasculitis. Clin Immunol 2008; 128: 39–45
56. Kamesh L, Heward JM, Williams JM *et al.* CT60 and +49 polymorphisms of CTLA 4 are associated with ANCA-positive small vessel vasculitis. Rheumatology (Oxford) 2009; 48: 1502–1505
57. Muzes G, Sipos F. Relation of immune semaphorin/plexin signaling to carcinogenesis. Eur J Cancer Prev 2014; 23: 469–476
58. Wieczorek S, Holle JU, Cohen Tervaert JW *et al.* The SEM6A6 locus is not associated with granulomatosis with polyangiitis or other forms of antineutrophil cytoplasmic antibody-associated vasculitides in Europeans: comment on the article by Xie *et al.* Arthritis Rheumatol 2014; 66: 1400–1401
59. Murakozy G, Gaede KI, Ruprecht B *et al.* Gene polymorphisms of immunoregulatory cytokines and angiotensin-converting enzyme in Wegener's granulomatosis. J Mol Med (Berl) 2001; 79: 665–670
60. Bartfai Z, Gaede KI, Russell KA *et al.* Different gender-associated genotype risks of Wegener's granulomatosis and microscopic polyangiitis. Clin Immunol 2003; 109: 330–337
61. Caruso C, Candore G, Cigna D *et al.* Biological significance of soluble IL-2 receptor. Mediators Inflamm 1993; 2: 3–21
62. Fontenot JD, Rasmussen JP, Gavin MA *et al.* A function for interleukin 2 in Foxp3-expressing regulatory T cells. Nat Immunol 2005; 6: 1142–1151
63. Lakshmikanth T, Burke S, Ali TH *et al.* NCRs and DNAM-1 mediate NK cell recognition and lysis of human and mouse melanoma cell lines in vitro and in vivo. J Clin Invest2009; 119: 1251–1263
64. Smith KG, Clatworthy MR. FcgammaRIIB in autoimmunity and infection: evolutionary and therapeutic implications. Nat Rev Immunol 2010; 10: 328–343
65. Dijstelbloem HM, Scheepers RH, Oost WW *et al.* Fcgamma receptor polymorphisms in Wegener's granulomatosis: risk factors for disease relapse. Arthritis Rheum 1999; 42: 1823–1827
66. Tse WY, Abadeh S, McTiernan A *et al.* No association between neutrophil FcgammaRIIa allelic polymorphism and anti-neutrophil cytoplasmic antibody (ANCA)-positive systemic vasculitis. Clin Exp Immunol 1999; 117: 198–205
67. Niederer HA, Willcocks LC, Rayner TF *et al.* Copy number, linkage disequilibrium and disease association in the FCGR locus. Hum Mol Genet 2010; 19: 3282–3294
68. Barnes BJ, Moore PA, Pitha PM. Virus-specific activation of a novel interferon regulatory factor, IRF-5, results in the induction of distinct interferon alpha genes. J Biol Chem 2001; 276: 23382–23390
69. Kawasaki A, Inoue N, Ajimi C *et al.* Association of IRF5 polymorphism with MPO-ANCA-positive vasculitis in a Japanese population. Genes Immun 2013; 14: 527–529
70. Popa ER, Stegeman CA, Abdulahad WH *et al.* Staphylococcal toxic-shock-syndrome-toxin-1 as a risk factor for disease relapse in Wegener's granulomatosis. Rheumatology (Oxford) 2007; 46: 1029–1033
71. Klotman ME, Chang TL. Defensins in innate antiviral immunity. Nat Rev Immunol 2006; 6: 447–456
72. Zhou XJ, Cheng FJ, Lv JC *et al.* Higher DEFB4 genomic copy number in SLE and ANCA-associated small vasculitis. Rheumatology (Oxford) 2012; 51: 992–995
73. Persson U, Truedsson L, Westman KW *et al.* C3 and C4 allotypes in anti-neutrophil cytoplasmic autoantibody (ANCA)-positive vasculitis. Clin Exp Immunol 1999; 116: 379–382
74. Walsh M, Chaudhry A, Jayne D. Long-term follow-up of relapsing/refractory anti-neutrophil cytoplasm antibody associated vasculitis treated with the lymphocyte depleting antibody alemtuzumab (CAMPATH-1H). Ann Rheum Dis 2008; 67: 1322–1327
75. Franssen CF, Stegeman CA, Kallenberg CG *et al.* Antiproteinase 3- and anti-myeloperoxidase-associated vasculitis. Kidney Int 2000; 57: 2195–2206
76. de Joode AA, Sanders JS, Stegeman CA. Renal survival in proteinase 3 and myeloperoxidase ANCA-associated systemic vasculitis. Clin J Am Soc Nephrol 2013; 8: 1709–1717
77. Quintana LF, Perez NS, De Sousa E *et al.* ANCA serotype and histopathological classification for the prediction of renal outcome in ANCA-

associated glomerulonephritis. Nephrol Dial Transplant 2014; 29: 1764–1769
78. Franssen C, Gans R, Kallenberg C *et al*. Disease spectrum of patients with antineutrophil cytoplasmic autoantibodies of defined specificity: distinct differences between patients with anti-proteinase 3 and anti-myeloperoxidase autoantibodies. J Intern Med 1998; 244: 209–216
79. Arulkumaran N, Periselneris N, Gaskin G *et al*. Interstitial lung disease and ANCA-associated vasculitis: a retrospective observational cohort study. Rheumatology (Oxford) 2011; 50: 2035–2043
80. Lionaki S, Blyth ER, Hogan SL *et al*. Classification of antineutrophil cytoplasmic autoantibody vasculitides: the role of antineutrophil cytoplasmic autoantibody specificity for myeloperoxidase or proteinase 3 in disease recognition and prognosis. Arthritis Rheum 2012; 64: 3452–3462
81. Suppiah R, Judge A, Batra R *et al*. A model to predict cardiovascular events in patients with newly diagnosed Wegener's granulomatosis and microscopic polyangiitis. Arthritis Care Res 2011; 63: 588–596

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