

## Systemic vasculitides: Immunogenetics and familial clustering

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### ABSTRACT

The systemic vasculitides (SV) are a heterogeneous group of rare affections characterized by a primary process of inflammation and damage of the blood vessel wall. Their etiopathogenesis is still unknown, but a complex interaction of multiple factors, such as age, sex, ethnic background, immunogenetic mechanisms and environmental influences, is probably involved. A genetic predisposition to SV is suggested by both familial case clusters and immunogenetic studies. The available reports on familial SV via the PubMed (National Library of Medicine) and Biosis indices, as well as personal observations, are summarized here. Furthermore, the evidence for a role of genetic predisposing factors is reported. The literature review suggests that several SV, such as giant cell arteritis, Takayasu arteritis, Kawasaki disease, Wegener's granulomatosis and Henoch-Schönlein purpura, are governed by multiple genes encoding host defence molecules and probably triggered by environmental agents. Genetic factors seem to be implicated not only in the susceptibility, but also in the severity and outcome of SV.

### Introduction

The systemic vasculitides (SV) are a heterogeneous group of rare affections, characterized by a primary process of inflammation and damage of the blood vessel wall, resulting in blood flow impairment and, ultimately, in ischaemia of the supplied tissues (1). SV may exhibit correlations with age, sex, ethnic origin and geographic distribution, as well as distinct tissue tropism, involving vessels of definite site and size (1). On the other hand, vasculitic processes with very similar histological features and anatomical distribution may determine highly heterogeneous phenotypes and outcomes, likely due to individual differences in the immuno-

modulatory milieu that may be genetically determined (2).

Although their etiopathogenesis is still unknown, SV probably represent the result of a specific immune response to hitherto unidentified triggering agents in predisposed subjects. The genetic predisposition to SV is supported by several findings, such as associations with human leukocyte antigens (HLA), evidence of the involvement of other immune response controlling genes, and familial clustering (3). The familial recurrence usually concerns the same type of vasculitis (3), whereas the aggregation of different SV is very rare (4-6). Familial cases generally occur in first-degree relatives (3), rarely in distant family members (7, 8). The SV concordance in mono- and dizygotic twins has a particular genetic relevance (3).

In this paper, the available reports on the immunogenetic predisposing factors for SV and familial clustering, as well as personal observations, are reviewed.

A detailed search via the PubMed (National Library of Medicine) and Biosis indices, was carried out using the following key terms: HLA typing, gene polymorphisms and immunogenetics of systemic vasculitides, familial systemic vasculitides, and familial clustering of systemic vasculitides. The information obtained is reviewed and summarized here. The SV are listed in accordance with the Chapel Hill Consensus Conference (CHCC) definitions (9); however, some familial case reports appeared before the CHCC nomenclature was published.

### Large vessel vasculitides

#### 1. Giant cell arteritis

Giant cell arteritis (GCA) is a granulomatous arteritis of the aorta and its major branches which shows a predilection for the extracranial branches of the carotid artery and commonly involves the temporal artery (9). GCA is closely related to polymyalgia rheum-

**Table I.** Familial cases of GCA and PMR: HLA typing and kindred relationship.

Study	Relationship	Diagnosis	HLA typing
Barber (15)	Sister	PMR	-
	Sister	PMR	-
Hamrin (16)	Sister	GCA	-
	Sister	GCA	-
Wadman (17)	Sister	GCA	-
	Brother	GCA	-
Liang (18)	Mother	GCA	-
	Daughter	GCA	-
	Sister	GCA	-
	Sister	GCA	-
	Mother	GCA	-
	Daughter	PMR	-
	Sister	PMR	-
	Sister	PMR	-
Kemp (19)	Twin sister*	GCA	A9,w26;B12,27;Cw3,w5
	Twin sister*	GCA	idem
Kvernebo (20)	Sister	PMR	A1,3;B8,27;Cw4
	Sister	PMR	A1,2;B8,27;Cw2
	Sister	PMR	-
Granato (21)	Father	GCA	-
	Daughter	GCA	-
Ninet (22)	Brother	GCA	A28,x;B15,x,B15,x;DR4,x
	Sister	GCA	A28,2;B15,8;Cw3,x;DR4,3
	Sister	GCA	A28,2;B15,12;Cw3,x;DR4,5
Tanenbaum (23)	Sister	GCA	-
	Sister	GCA	-
Mathewson (24)	Brother	GCA	A1,2;B8,26,w62;Cw3,w7;DR3,4,w52,w53
	Brother	GCA	A2,28;B w4,w6,w44,w62;Cw3,w7;DR4,w53
Wernick (25)	Sister	GCA	A1,24;B8,62;DR3,4
	Brother	GCA	idem
Schwizer (26)	Sister	GCA	A3,28;B55,60;Cw3;DQ1,3;DR4,13,52,53
	Sister	GCA	idem
	Sister	GCA	A2,24;B35,39;Cw4;DQ1,3;DR1,4
	Brother	GCA	A2,x;B13,39;Cw6;DQ2;DR7,DRx,DR53
Zauber (27)	Father	GCA	-
	Daughter	GCA	DR3, DR4
Gros (28)	Sister	GCA	A1,26;B8,18;DR15,17
	Sister	GCA	A1,29;B8,27;DR1(DRB1*0103),DR17
Bartolome (29)	Sister	GCA	DRB1*04(DRB1*0401) / DRB1*12
	Brother	GCA	DRB1*07 / DRB1*12
Fietta (30)	Sister	GCA	both shared the genotype A*24,*26; B*38,*55;
	Sister	GCA	DQB1*05,*07;DRB1*11,*14,DRB3*
	Sister	GCA	-
	Sister	PMR	A*02,*68;B*44,*51;DQB1*05,*07;DRB1*01,*11,DRB3*
	Brother	PMR	A*01,*68;B*15,*44;DQB1*07,*08;DRB1*04,*11,DRB3*,DRB4*

\* Monozygotic twins. This table is reproduced with permission from P. Fietta *et al.*: Familial giant cell arteritis and polymyalgia rheumatica: aggregation in 2 families. *J Rheumatol* 2002; 29: 1551-5.

atICA (PMR) (9,10), an inflammatory affection sharing a similar, but subclinical vasculitic nature (11,12), so that they have been considered as two phases of the same disease (10), probably corresponding to different patterns of cytokine production (13). Both GCA and PMR primarily affect white people older than 50 years, mostly of Caucasian origin and in northern countries (10). The strict age of onset has been established as a diagnostic criteria (10). The etiopathogenesis of GCA/PMR is still unknown. The role of environmental factors is controversial (10); however, data support the model that GCA is an antigen-driven disease (14).

Increasing evidence indicates that genetic factors are determinant in both GCA and PMR susceptibility. As a matter of fact, familial clusters of GCA and PMR have been reported by several authors (15-30) (Table I). In most cases, the described relationship has been between siblings (15-20, 22-26, 28-30); however, mother-daughter (18) and father-daughter (21,27) recurrences have also been found (Table I). A report of monozygotic twin sisters concordant for GCA whose respective disease onset was separated by a period of several years (19), and another report of a pair of monozygotic twin sisters living together but discordant for PMR over an observation period of 7 years (31), underline the complexity of the involved pathogenic factors.

Notwithstanding variable results due to the different ethnic backgrounds of the studied populations (32-34), GCA and PMR have been associated with HLA-DR4 (35-40). Moreover, most studies have found that GCA is an HLA-DRB1-related affection (41-43). Clinical features of severe disease, such as visual complications, have been associated with the HLA-DRB1\*04 allele (44). In GCA French patients, HLA-DRB1\*04 has been identified as a possible marker of corticosteroid resistance (45). PMR concomitant with GCA seems to be closely associated with HLA-DRB1\*04, while isolated PMR is variably related to the HLA-DRB1\*04, \*01 and \*13,\*14 alleles in different populations (43,46-49). Relapses of PMR are significantly more

frequent in Spanish patients carrying the DRB1\*04 allele and, in particular, DRB1\*0401 (50).

In North American patients, a conserved amino acid (AA) sequence (28 DRYF 31) within the second hyper-variable region of the DRB1 allele has been proposed as a susceptibility marker for GCA/PMR (41, 42). A hierarchy of HLA-DRB1 alleles predisposing for GCA has been suggested, with DRB1\*0401 appearing to be the strongest risk factor (41). In other populations, however, this hypothesis has not been confirmed (47, 48, 51, 52).

Recently, we described the aggregation of both GCA and PMR in 2 unrelated families living in northern Italy (30). Two sisters in the first family, who were concordant for GCA, shared the same genotype, carrying DQB1 \*05, \*07, DRB1 \*11, \*14, and DRB3\* alleles (Table I). In the second family, a sister had GCA and, two years later, her brother and sister developed PMR nearly simultaneously. The PMR patient genotypes shared the DQB1 \*07, DRB1 \*11, and DRB3\* alleles (Table I). Thus, the patients of both families shared not only DQB1\*07 and DRB3\*, but also DRB1 \*11, which is one of the DRB1 alleles carrying the DRYF tetrapeptide.

Immunogenetic polymorphisms may act as susceptibility factors to GCA and PMR. In some populations gene polymorphisms for tumor necrosis factor (TNF)- (53, 54), ICAM-1 (intercellular adhesion molecule-1) (55, 56), RANTES (regulated upon activation normal T cell expressed and secreted) (57), and IL-1ra (interleukin-1 receptor antagonist) (54) may play a pathogenic role. On the other hand, in Spanish biopsy-proven patients GCA seems to be independent of the polymorphism of the IL-1 locus and TNF- gene (58). In such a cohort of patients, these cytokine polymorphisms are not implicated in the risk of ischaemic visual complications (58). In biopsy-proven GCA Spanish patients not carrying the HLA-DRB1\*04 alleles, the IL-6 promoter polymorphism at position -174 modulates the phenotypic expression of PMR (59). In GCA Spanish patients, the corticotropin-releasing hormone A2

allele may encode the risk for developing visual complications (60). In Danish patients, mannose-binding lectin (MBL) variant alleles not only confer increased susceptibility to GCA, but are also associated with high inflammatory activity and clinical signs of arteritic manifestations (61). Furthermore, in Italian studies the Glu/Asp<sup>298</sup> polymorphism of the endothelial nitric oxide synthase gene is associated with GCA susceptibility (62), as well as the carriage of C(cytosine)634 and I(insertion) alleles in the vascular endothelial growth factor gene (63).

Otherwise, the nucleotide polymorphism in the A561C E-selectin gene is not related to GCA(64).

## 2. Takayasu arteritis

Takayasu arteritis (TA) is a granulomatous inflammation of the aorta and its major branches (9). TA usually occurs in women younger than 50 years (9), and has a worldwide distribution, although a higher frequency has been reported in the Far East and South America (65). Differences in disease expression and outcome in different countries and ethnic groups have been observed (65, 66).

The etiopathogenesis of TA is still unknown. A relationship between TA and infectious agents has been suggested (65). Genetic studies have shown that HLA-B alleles are involved in the disease susceptibility. HLA-B52 is associated with TA in Korean (67), Japanese (68), Northern Indian (69), Thai (70) and Mexican Mestizo (71) populations. In Arab patients, the presence of HLA-A2, A9, Bw35 and DR7 alleles has been reported (72). In addition, in North American studies a positive correlation with HLA-DR4/MB3 (DQw3) (73) and a strongly negative association between DR1 (74) and TA were found.

In Asian populations, HLA-B52 (B\*5201) and B39 (B\*3901 and B\*3902) alleles not only are associated with the disease (68,69, 75), but also may determine different clinical manifestations (75) and outcomes (76). Such disease-related alleles share AA residues at position 63 (glutamic acid) and 67 (serine) (68). Moreover, in Mexican Mestizo patients a positive association with

both HLA-B52 and B15 was found (71). Interestingly, the disease-related antigens of both Asian and Mexican Mestizo patients share one or two of the above mentioned AAre residues (77). Thus, these shared epitopes, which belong to an antigen binding-site (pocket B) in the HLA-B molecule, may be critical for TA susceptibility (71). In the same Mexican patient cohort, a significant correlation between HLA-DR14 and the presence of systemic arterial hypertension, as well as between HLA-A2 and the pulmonary arterial involvement, was observed (71).

Immunogenetic polymorphisms have been carefully investigated in Japanese TA patients (78-80). Studies on the polymorphisms of human complement factor 4 (C4) showed a significantly high frequency of C4A2 and C4BQ0 allotypes in strong association with HLA-Bw52 (78). Typing of the major histocompatibility complex class I chain-related (MICA) gene, located near the HLA-B gene, revealed that the MICA-1.2 allele is significantly associated with TA, providing a high risk for development of the disease, even in the absence of HLA-B52 (79). Analyses of the polymorphisms in five microsatellites, C1-2-A, MIB, C1-4-1, C1-2-5, C1-3-1, around the HLA-B and MICA genes, have suggested the existence of two susceptibility loci for TA, one mapped near the C1-2-A locus and the other more closely linked to the HLA-B than to the MICA gene, because there are at least two different disease-related HLA-B haplotypes, HLA-B\*52 and B\*39.2, which share the TA-associated C1-2-A allele (80).

Familial aggregations of TA have been reported, mostly between siblings (81-83) or twins (84, 85), but also in one case involving a Caucasian mother and her daughter (86) (Table II). The recurrence of TA in monozygotic twin sisters (84, 85) and in male siblings (81, 82), including a pair carrying an identical genotype (82) (Table II), underlines the role of genetic predisposition. However, HLA typing carried out in these familial cases did not elicit any consistent associations (Table II), thus supporting the hypothesis that TA genetic susceptibility may be multi-factorial.

### Medium-sized vessel vasculitides

#### 1. Polyarteritis nodosa

Polyarteritis nodosa (PAN) is a necrotizing inflammation of the medium-sized or small arteries, without glomerulonephritis or vasculitis in the arterioles, capillaries and venules (9). Classic PAN, as defined by CHCC (9), appears to be very rare (87). The disease is observed in all racial groups and affects equally both sexes at every age, with a predominance between 40-60 years (88).

The etiopathogenesis of PAN is unknown. The role of infectious triggers has been proposed (88-90). Presently, there is no clear evidence of specific HLA associations. An interesting finding is the complete absence of the

HLA-DR3 allele in Greek PAN patients, contrasting with a 17% prevalence of this antigen in the whole Greek population (91). Thus, this allele might have a protective role (91).

Cases of familial clustering of PAN have been reported (5,92-96) (Table III), most of them before the publication of the CHCC nomenclature (9). Recurrences have been observed between siblings (5, 92, 94, 96), monozygotic twin sisters (93), and also between a father and son (95) (Table III). HLA typing did not elicit any conclusive associations (Table III).

#### 2. Kawasaki disease

Kawasaki disease (KD) is an arteritis involving the large, medium-sized and

**Table II.** Familial cases of TA: HLAtyping and kindred relationship.

Study	Relationship	HLAtyping
Numano (84)	Twin sister*	A9,*11;B5,w40
	Twin sister*	idem
Makino (81)	Brother	A2,9;Bw15,w35;Cw3,x;DRw4,w8
	Brother	A9,11;Bw52,w54;Cw1,x;DRw2,w4
Enomoto (85)	Twin sister*	-
	Twin sister*	-
Kodama (82)	Brother	A2,24(9);B40,w59;Cwl;DR2,DR4
	Brother	idem
Valentini (86)	Mother	A24;Bw6,16;DR1,DR2
	Daughter	A11,24;Bw6,35;Cw4;DR4
Naik (83)	Sister	-
	Sister	-

\*Monozygotic twins

**Table III.** Familial cases of PAN: HLAtyping and kindred relationship.

Study	Relationship	HLAtyping
Schneider (92)	Brother	-
	Sister	-
Harris (93)	Twin sister*	-
	Twin sister*	-
Leff (94)	Sister	-
	Brother	-
Reveille (95)	Father	A2;B7,X;DQw1;DRX
	Son	A2;B44,X;DQw1,w3;DR4,w53,X
Mason (96)	Brother	A11,28;B5,12;DQw7;DR5
	Sister	A11,31;B5;DQw7;DR4,5
Rottem (5)	Sister	A2,26;B51,57;Cw1,w6;DQ5,9;DR1,7,DR-,53
	Sister	A2;B18,57;Cw-,w6;DQ2,7;DR7,11,DR52,5
	Sister	A2;B18,57;Cw-,w6;DQ2,7;DR7,11,DR52,53

\*Monozygotic twins

small arteries, associated with mucocutaneous lymph node syndrome, and particularly affecting children (9,97). The coronary arteries are typically involved, with potential aneurysm formation (98). Although KD occurs worldwide, it is most prevalent in children of Japanese descent, and may present in both the endemic and epidemic form (99). The etiopathogenesis of the disease is unknown, but various infectious and non-infectious triggering agents have been proposed (98).

Several studies underline a genetic susceptibility to KD. The incidence of KD in siblings is much greater than in the general population (100). In the familial cases, KD mostly occurred between first-degree relatives such as siblings (101, 102), dizygotic (103) and monozygotic twins (104), mother/son (105, 106), mother/daughter (107), father/son (108) and father/daughter (109), but also between two cousins (7) (Table IV). In two identical twins, KD developed simultaneously (104). HLA typing did not provide conclusive findings, however (Table IV).

In Japanese patients, HLA-Bw15 and Bw22 (especially the Bw22J2 subtype) were reported to be associated with KD in one study (110), but not in another (111). A weak association with HLA-Bw51 has been observed in Israeli patients (112) and in non-Jewish Caucasian patients in New England (113). In Caucasian patients, a prevalence of HLA-Bw51 during periods of endemic KD, and of HLA-Bw44 during the epidemic phase, was observed (114). In KD no consistent role for the major histocompatibility complex class II alleles was found (115). Moreover, some immunoglobulin (Ig) allotypic markers were over-represented among white, but not Japanese patients (116).

Immunogenetic polymorphisms seem to play an important role in susceptibility to KD. In the Japanese population, the high prevalence of the G (guanine) allele in the distal regulatory region of the monocyte chemoattractant protein (MCP)-1 gene suggests a potentially crucial ethnic variation in MCP-1 production (117), whose role is considered to be relevant in the pathogenesis of KD (118). Furthermore, KD patients

**Table IV.** Familial cases of KD: HLA typing and kindred relationship.

Study	Relationship	HLA typing
Schnaar (7)	Cousin	-
	Cousin	-
Fink (104)	Twin*	-
	Twin*	-
Hewitt (101)	Sister	-
	Brother	-
Iwata (108)	Father	A2,24;Bw62;Cw3
	Son	A24;Bw60,w62;Cw3
Matsubara (102)	Brother	A2,24;Bw46,51;Cw11;DR4,DRw8
	Brother	A2,24;Bw46,51;Cw11;DR4,DRw8
	Sister	A2,2;B39,w46;Cw7,w11;DRw8,DR9
Kaneko (103)	Twin°	-
	Twin°	-
Segawa (105)	Mother	A2,26;B51,52;DQ3,DQ6;DR8,DR9
	Son	A2;B46,51;Cw1;DQ3,DQ6;DR8,DR9
Bruckheimer (106)	Mother	-
	Son	-
Kaneko (109)	Father	A2,24;B7,35;Cw3,w7;DR2,DR9
	Daughter	A2,31;B35,52;Cw3;DR6,DR9
Mori (107)	Mother	A2,24(9);B51(5),52(5);DR12(5),DR2
	Daughter	A2,24(9);B39(16),52(5);Cw7;DR4,DR2

\*Monozygotic twins; °dizygotic twins.

carrying the -2518 G allele of the MCP-1 gene seem to run a greater risk of coronary aneurysms, despite gamma globulin therapy (117). Allele 1 of the SLC11A1 gene, formerly called the natural resistance-associated macrophage protein 1 gene, is highly represented in Japanese KD patients (119), and the angiotensin I converting enzyme (ACE) genotype II is associated with the development of coronary lesions (120). White, but not Japanese children with KD were found to have a significantly higher frequency of the A(adanine)/A genotype at the lymphotxin- +250 site than a control population, and the TNF- -308 A/G genotype is increased in white patients with coronary artery abnormalities (121). Both of these genotypes are associated with higher TNF-

serum levels after an inflammatory stimulus (121). Studies on the microsatellite polymorphism of the transmembrane region of the MICA gene showed that the A4 allele was negatively associated with the formation of coronary aneurysms, while the frequency of A5 tended to be higher in patients who developed aneurysms (122).

Moreover, the T(thymine)/T genotype of the methylenetetrahydrofolate reductase gene seems to protect KD female patients against initial aneurysm development and, otherwise, predispose KD male patients to severe coronary complications (123). In white Dutch children with KD, the frequency of MBL gene mutations is higher than in controls, and patients younger than 1 year of age with mutations are at greater risk of coronary artery lesions than those without (124).

### Small vessel vasculitides

#### 1. Wegener's granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis (antineutrophil cytoplasmic antibodies-associated vasculitides)

Wegener's granulomatosis (WG), Churg-Strauss syndrome (CSS) and microscopic polyangiitis (MPA) (as well as renal limited vasculitis which, however, has not been included in the CHCC definition) (9) constitute a subset of small vessel SVusually associated with the presence of antineutrophil cytoplasmic antibodies (ANCA) in the serum (9). The diagnostic relevance of

ANCA is widely accepted, while their pathogenic role is debated, but increasingly recognized (125-129).

Environmental factors such as infectious agents (130) or exposure to dust (131), silica (132) or drugs (133) have been suggested as possible triggering agents of ANCA-associated SV (AASV). Presently, the most clearly identifiable exogenous triggering factor is the anti-thyroid drug propylthiouracil (133).

The role of genetic factors in AASV susceptibility is suggested by reports on familial clusters and data on the association of AASV with the polymorphic variants of proteins such as -1-antitrypsin (-1-AT), the main inhibitor of proteinase 3 (PR3) (134-136). The incidence of the deficient -1-AT phenotype in ANCA-positive patients is probably low, but its clinical relevance is emphasized by their poorer outcome (134).

In AASV patients, cytoplasmic ANCA positivity is associated with the Z allele, whereas perinuclear ANCA positivity is associated with the S allele of the -1-AT gene (137). In German AASV patients, no major differences in the distribution were observed for the IL-2 and IL-5 receptor gene microsatellites, nor for polymorphisms of the TNF- $\alpha$  promoter (TNF-308) and the coding region for the Fc gamma fragment receptor (Fc R) IIa (138). The characterization of the neutrophil antigen (NA) NA1/NA2 polymorphism of the Fc RIIIb gene, which affects the functional capacities, showed significant over-representation of the homozygosity for the NA1 allele (higher net function) in AASV patients with myeloperoxidase (MPO)-ANCA (139).

In an AASV patient cohort, studies of the C3 and C4 allotypes showed an increased frequency of C4A3 in the whole patient group, and of the C3F allele in the PR3-positive subgroup (140). Studies of CD18, a key molecule of the adhesion cascade expressed by polymorphonuclear granulocytes, have demonstrated that CD18 gene polymorphisms are associated with the MPO-positive vasculitides (141,142). -463 G/AMPO promoter polymorphism is related to the incidence and disease course of MPO-associated vasculitides (143). Indeed,

the GG genotype is significantly associated with an increased risk of the disease in females but not in males, and the MPO A allele is associated with a higher relapse rate and an earlier age at diagnosis (143).

In PR3-AASV patients, the pro-inflammatory IL-1 $\beta$ /IL-1ra genotype is associated with an increased risk of developing end-stage renal disease (ESRD) (144).

To date HLA typing studies have not provided definite associations in AASV. Reports indicating positive associations with HLA-DR1, DR2, DR4, DQ7 and DR8, negative associations with DR3 or DR13, or even no significant associations at all, have been published (145-148). A slightly decreased representation of HLA-DQB1\*0603 and HLA-DRB1\*13 was observed in a cohort of AASV German patients compared to controls (138).

The specific immunogenetic studies for each ANCA-associated vasculitis, as well as the relative familial cases, are reported below.

a) Wegener's granulomatosis. WG is a granulomatous inflammation involving the respiratory tract and a necrotizing vasculitis affecting the small to medium-sized vessels (9). WG is commonly associated with PR3-ANCA (125,126, 128, 129). It predominates among middle-aged Caucasians of both sexes, Afro-Americans being relatively underrepresented (149).

The etiopathogenesis of WG is presently unknown. The occurrence of the disease in subjects exposed to dust (131) and to silica compounds (150,151), as well as in unrelated members of the same family (152), underlines the role of environmental factors. Infectious agents may be implicated in the pathogenesis of WG (130,153,154) and in triggering its relapses (154,155).

A genetic predisposition to WG is suggested by several findings. Firstly, the membrane expression on neutrophils of PR3, the main target antigen of ANCA in WG, is genetically determined (156). An association with WG has been demonstrated for a polymorphism in the PR3 promoter region, affecting a putative transcription factor-binding site

which may allow PR3 overexpression (127,157). Moreover, studies on gene polymorphisms of the PR3 inhibitor -1-AT have been carried out, showing that defective genotypes are strongly related to WG (134,158,159) and its outcome (160). A linkage disequilibrium between genes at the serine protease inhibitor gene cluster on chromosome 14q32.1 is associated with WG (161).

In Swedish Caucasian patients, an AT repeat polymorphism in the 3' untranslated region of exon 3 in the cytotoxic T lymphocyte antigen 4 (CTLA-4) gene (*Ctla-4*), encoding for a protein that downregulates the immune response but not the polymorphism in TNF- $\alpha$  or IL-1 $\beta$  genes, is strongly associated with the disease (162). Similarly, a close association between WG and a C/T single nucleotide polymorphism in the *Ctla-4* promoter region at position -318 was found (163). Although in WG patients the TNF gene polymorphisms did not statistically differ from controls, TNF 1/1 patients were found to have a higher mean disease extension index (164). In Swedish Caucasian patients, a C/A dinucleotide repeat polymorphism in the promoter region of IL-10 gene, *IL-10.G*, was associated with the disease (165). In another study on Caucasians, a significant shift toward the homozygous AA genotype of the IL-10 (-1082) polymorphism was also found in WG patients, with no difference between genders seen (166). Furthermore, a trend to the low producer genotype CG of the transforming growth factor- $\beta$  gene was demonstrated in WG (167), but not confirmed in a larger cohort of patients (166).

Fc R allelic polymorphisms seem to be related to the outcome of WG. Fc RIIa-H131/R131 and Fc RIIIb-NA1/NA2 alleles may alter disease severity and/or phenotype (168), the NA1 allele being strongly associated with significant renal involvement (169). Both the R/H131 polymorphism of Fc RIIa and the V/F158 polymorphism of the Fc RIIIa gene seem to represent heritable risk factors for disease relapses (170). Otherwise variants of the NOD2/CARD 15 gene, a member of the NOD1/apop-

**Table V.** Familial cases of WG: HLA typing and kindred relationship.

Study	Relationship	Diagnosis	HLA typing
Muniain (179)	Sister	WG	-
	Sister	WG	-
Knudsen (180)	Brother	WG	shared haplotype A2;B7;DRw12
	Brother	WG (?)	
Ten Hacken (181)	Mother	WG	-
	Daughter	WG	-
Hay (182)	Brother	WG	A3,10;B8,17;DR3,DR7
	Sister	WG	A3,10;B8;DR3,DR4
Stoney (183)	Brother	WG	A3,31;B14,w60;DR4,DRw6
	Brother	WG	A11,31;B44,w60;DR4,DRx
Sewell (184)	Mother	WG	A9,11;B14,18;DR1,DR2
	Daughter	WG	A2,9;Bw4,w6,12,14;DR1
Nowack (8)	Nephew	WG	-
	Uncle (4th degree relative)	WG	A2,11;B14,22;Cw1;DQ1,DQ5;DR1,DR2
	Aunt (2nd degree relative)	WG	-

totic protease-activating factor-1 gene family, are not associated with WG (171).

HLA typing studies on different populations have shown an increase of HLA-B7 (172), B8 (172-174), B50 and DR9 (175,176), DQw7 (145), DR2 (174), DR4DQ7 (148), and a highly significant increase of HLA-DR1 in WG (91,177). The combined frequency of DR1-DQw1 was found to be higher in patients than in controls (177). In contrast, HLA-DR3 (145, 148) and HLA-DR13DR6 (178) were under-represented in WG, while HLA-DRB1\*04 was over-represented in a subgroup of ESRD patients (138).

Familial clustering of WG cases have been described (8, 179-184) (Table V). The most frequent recurrence was observed in first-degree kindred (179-184), but in one family three 2nd and 4th degree relatives were found suffering from WG and an ancestor had died due to an unspecified pulmonary disease (8). In these familial cases, however, HLA typing yielded inconclusive results (Table V).

b) Churg-Strauss syndrome. CSS is an eosinophil-rich granulomatous inflammation involving the respiratory tract, and a necrotizing vasculitis affecting the small to medium-sized vessels, associated with asthma and eosinophilia (9). Patients are usually middle-aged,

with a male-to-female ratio ranging from 1.1 to 3 (88). ANCA are detectable in 48-66% of CSS patients (185), MPO and to a lesser extent PR3 being the target antigens (125,126, 128, 129). The etiopathogenesis of CSS is still unknown. Precipitating factors for CSS may be allergens, parasites, infections, exposure to drugs, parenteral vaccination or desensitisation regimens (185, 186). In asthmatic patients, cysteinyl leukotriene receptor antagonists (185-187), as well as other systemic steroid sparing medications (185,187), have been reported to trigger the disease. However, the development of CSS may be related to the corticosteroid withdrawal itself unmasking a pre-existing pathologic condition (185, 187), rather than to a direct drug effect.

To date no consistent genetic associations have been found in CSS patients. Preliminary evidence of a higher frequency of HLA-DR2 in CSS has not been confirmed (174). The incidence of DR4DQ7 was found to be significantly increased in Caucasian CSS patients (148) compared to the general population. On the other hand, the absence of DR3 in CSS Greek patients has been reported (91).

No familial clustering of CSS has hitherto been reported.

c) Microscopic polyangiitis. MPA is a necrotizing vasculitis with little or no

immune deposits, affecting the small vessels (i.e. arterioles, capillaries and venules) (9). Necrotizing glomerulonephritis is very common; pulmonary capillaritis often occurs (9, 88, 188). The average age at onset is about 50 years, with a male-to-female ratio ranging from 1 to 1.8 (88). In MPA, MPO-ANCA have been reported in 40-80% of the cases and PR3-ANCA in a lesser percentage (125, 126, 128, 129).

The etiopathogenesis of the disease is unknown. The role of environmental factors is debated (189,190). So far HLA typing studies have not provided any definite association. An increase in HLA-A26 and HLA-A11, as well as a decreased frequency of HLA-DR3, have been reported in Greek MPA patients (191). In this study, 5 of 6 patients not responsive to immunosuppressive treatment carried HLA-DR5 (191). In British patients, HLA-DQw7 was increased and HLA-DR3 was decreased compared to controls (145). In Japanese AASVpatients, HLA-DRB1\*0901 was associated with MPA (192). As in Caucasian WG patients, the biallelic polymorphism at position -1082 of the IL-10 gene showed a significant trend toward the homozygous AA genotype, that furthermore in MPA patients proved to be significantly more frequent in females than in males (166).

Familial clustering of MPA has been

**Table VI.** Familial cases of MPA: HLA typing and kindred relationship.

Study	Relationship	HLA typing
Barbiano di Belgiojoso (195)	Father	A11,32;B35 X;Cw4 X
	Son	A11,26;B35,w55;Cw3,w4;DRw6 X
Heuze-Claudot (193)	Brother	-
	Sister	-
Franssen (194)	Brother	-
	Sister	-
Brener (150)	Brother	A24,29;B14,58;DQ5;DR1,DR16
	Brother	A2,29;B18,58;DQ3,DQ5,DQ7;DR11,DR16

described (150, 193-195) (Table VI). The familial recurrence was observed between siblings (150, 193, 194), and between a father and his son (195) (Table VI).

### 2) Henoch-Schönlein purpura

Henoch-Schönlein purpura (HSP) is a vasculitis with IgA-dominant immune deposits, affecting the small vessels and typically involving the skin, gut and glomeruli (9). HSP primarily occurs in children, with a median onset age of 6 years, whereas it is rare but usually more serious in adults (196). The etiopathogenesis of HSP is unknown. Exogenous triggering factors, such as viral, bacterial and parasitic infections, drugs, toxins, and systemic and neoplastic diseases, have been suggested (196,197). Reports of HSP relapses in patients who have undergone a renal transplant (198) as well as immunogenetic data underline a genetic predisposition. Studies on the HLA class III region showed an increased frequency of C4 gene deletions in Caucasian (199) and Japanese (200) patients with nephritis. In Korean patients, locus II deletion of C4, but not a C4B sequence loss, is a risk factor for nephritis and the deleted gene can be either C4A or C4B (201).

In an Italian study, HLA-DRB1\*07 was significantly less frequent in HSP patients than in controls, whereas 64% of patients expressed DRB1\*01 and/or DRB1\*11, compared with 48% of the control group (202). Among DRB1\*11 subtypes, DRB1\*1104 was significantly increased in HSP patients. Moreover, the presence of DRB1\*01 or DRB1\*11 alleles appeared to condition an earlier

disease onset (202). Similarly, in Spanish patients a significantly higher frequency of the HLA-DRB1\*01 allele and a significantly reduced expression of DRB1\*07 have been found compared to controls (203, 204). However, HLA-DRB1\*01 does not seem to be a genetic marker for disease severity. Indeed, in Korean (201) and Spanish (205) patients with renal complications, an increased frequency of HLA-DQA1\*0301 and B35, respectively, was observed. In addition, HSP patients carrying B35 showed recurrent episodes of nephritis, triggered by minor pharyngeal infections (206).

Both RANTES and epithelial cell-derived neutrophil-activating peptide (ENA-78) gene polymorphisms are not implicated in the HSP susceptibility and phenotype (207). The deletion (D) and I polymorphisms in intron 16 of the ACE gene were examined in HSP patients. The ACE DD genotype appears to predict persistent proteinuria in HSP patients with nephritis (208), but in other studies neither deletion (209) nor I/D polymorphisms (210) were associated with the disease severity.

The allele frequency and carriage rate of the IL-1ra allele 2 (*IL1RN\*2*) of the IL-1ra gene were found to be significantly higher in HSP patients with nephritis than in normal subjects or in patients with IgA nephropathy and acute post-infectious glomerulonephritis (211). The significant association between carriage of *IL1RN\*2* and severe renal disease was confirmed in another study (212). Moreover, an increased frequency of the A allele of the IL-8 gene was found in patients with renal involvement, compared to those without (207).

ICAM-1 gene polymorphism alone is not associated with the development of HSP, but notably patients not carrying the codon 469 lysine/glutamic acid genotype appear to have a significantly reduced risk of severe gastrointestinal complications (213). Furthermore, in adult HSP patients the arginine/glycine polymorphism at codon 241 of the ICAM-1 gene may have a protective effect on the risk of renal sequelae (213). Otherwise, the polymorphism in the E-selectin gene is not associated with HSP (64). HSP patients with -1-AT deficiency has been reported, but the deficient phenotype, rather than being an etiological risk factor seems to have an accelerative effect on the vasculitic process (214, 215).

Familial cases of HSP have been reported (216-219). The occurrence of HSP several years apart in three members of a family was described (216). In another family, three members suffered from HSP, in two of whom the disease onset followed streptococcal pharyngitis (217). Furthermore, it has been reported that two sisters simultaneously developed HSP, the day after wearing new slippers made of synthetic material and with no clinical evidence of infections (218). Finally, in another pair of siblings HSP with nephritis was observed following infectious mononucleosis (219).

### 3) Cryoglobulinemic vasculitis

Cryoglobulinemic vasculitis (CV) is a vasculitis with cryoglobulin immune deposits, affecting the small vessels and associated with cryoglobulins in the serum (9, 220, 221). Most cases of what was formerly referred to as "essential" mixed cryoglobulinemia (MC) or "essential" CV can actually be attributed to hepatitis C virus (HCV) infection (221), anti-HCV antibodies being found in 60-80% (222-224) and HCV RNA in 86% of "essential" MC patients (222). However, although 60-90% of HCV-infected subjects have cryoglobulins in their serum, only a small percentage exhibit a clinically symptomatic vasculitis (225).

The circumstances predisposing HCV-infected patients to the development of CV remain unclear. Studies have failed

to demonstrate a role of genomic viral factors, whereas host factors such as female sex and older age have been associated with CV (220). HLA typing was carried out in a group of Italian patients with HCV-positive MC, compared to those with HCV-related chronic active hepatitis (CAH) and normal controls (226). HLA-A9 with its split A24 was present in 50% of the MC patients, in 16.6% of those with CAH and in 16.8% of controls (226). Moreover, HLA-B51 and B35 showed a higher frequency in MC patients (31.2%), compared to the CAH and control groups. DR11 was highly expressed in both patient groups, whereas HLA-DR7 was found only in the CAH group (226). In Chinese patients with chronic hepatitis C and cryoglobulinemia, a significant increase in HLA-DR3 and DR4 was observed (227).

A significant association with HLA-DR3 and an even stronger association with HLA-B8 allele were found in Italian MC patients with HCV positivity, compared to controls (228). In another Italian study, the DRB1\*11 allele was significantly more frequent in HCV-infected MC patients than in controls, and appeared to be a protective factor for serious chronic liver disease (229). In this cohort, Ig heavy chain constant 1 switch region restriction length polymorphisms were associated with MC (229). Similarly, in HCV-infected French patients, HLA-DRB\*11 (DR11) was associated with less severe liver fibrosis and a significantly increased risk for the development of type II MC, whereas HLA-DR7 appeared to protect against type II cryoglobulin production (230).

Familial cases of cryoglobulinemia have been reported (231-233). In one family 4 sisters suffered from MC (231). In another family, 10 members of three generations were affected by MC; in these patients no linkage with HLA haplotypes or Ig allotypes was detected (232). Finally, in a third family, nine members had cryoglobulinemia and C4 deficiency; only this latter was HLA-linked (233).

**4) Cutaneous leukocytoclastic angiitis**  
This vasculitis, in the past also termed

"hypersensitivity vasculitis", is an isolated cutaneous leukocytoclastic angiitis (CLA), confined exclusively to the dermal small vessels, without extracutaneous features (9, 234). To make such a diagnosis, it is essential to exclude other SV with cutaneous involvement (9).

The etiopathogenesis of CLA is unknown. Histories of exposure to medications or infections are often present in CLA (234), but the role of exogenous factors remains elusive. A genetic predisposition to CLA has been suggested. In a Northwest Spain population, HLA-DRB1 genotype differences between CLA patients and healthy controls were not found, but, when DRB1 genotypes of CLA and HSP patients were compared, a significant increase of HLA-DRB1\*15/16 and especially of HLA-DRB1\*07 was found in those with CLA (204). Immune complexes of CLA patients bind to endothelial FcR independently of the allelic polymorphism of Fc RIIa (235).

From the literature review, presently, familial cases of CLA have not been reported.

#### Familial clustering of different types of SV

Familial clustering of different types of SV is very rare. In one family with hereditary C4 deficiency, the father with partial C4 deficiency suffered from WG, whereas his son with complete C4 deficiency presented HSP (4). The association in a single family of a case of PAN and two cases of WG has been reported (5). The 51-year-old father developed WG with a rapid, fatal outcome. Eight years later his 29-year-old son presented clinical features of hepatitis B virus-related PAN with a fatal outcome and 11 years later his 32-year-old daughter developed WG. HLA typing was performed only on the daughter (5).

Recently, we observed the occurrence of CSS in a 51-year-old man, and 5 years later of WG in his 33-year-old son, both living in a city in northern Italy (Milan) (6). To our knowledge, this is the first report of the aggregation of WG and CSS in the same family. Because our patients had upper or low-

er airway disease and both lived in an urban area, a role of environmental factors such as air pollution could be suggested. They shared the HLA haplotype A\*03, B\*07, C\*w07, DQB1\*0302, DRB1\*0404, and thus a genetic predisposition may play a strong role. However, although they were exposed to the same environmental milieu and shared a similar genetic background, they suffered from close, but clinically different forms of SV. Assuming that both of these AASV have a partial common polygenic background and that the son had inherited a common haplotype and other susceptibility genes from his father, probably other genes inherited from the mother could have had a modifying effect, producing a different clinical phenotype (6).

#### Conclusion

Familial clustering of a disease may occur by chance (especially for common affections) or due to exposure to the same environmental triggers, shared genetic susceptibility or a combination of these factors. Since the SV are relatively uncommon diseases, reports of familial clusters testify to a genetic predisposition, although to date significant HLA associations have been identified only for some SV, suggesting either that such affections are heterogeneous and polygenic or that the real immunogenetic relationships remain to be found. Moreover, the observed associations with polymorphisms of genes involved in the immune and inflammatory response may explain the variability of the clinical expression and outcome in patients with similar histological features and a similar anatomical distribution of the lesions.

In addition, the so-called "genetic anticipation" (236) in offspring of affected parents appears to have an insignificant role in SV susceptibility, unlike other genetically complex diseases or autoimmune affections (237), even if familial SV may show the tendency to start at an earlier age than usual (5, 94, 96, 179, 193).

Ultimately, immunogenetic studies and familial clustering suggest that several SV, such as GCA, TA, KD, WG and HSP, are governed by multiple genes

encoding host defence molecules, and probably triggered by environmental agents. Such genetic factors seem to be implicated not only in susceptibility, but also in disease severity and outcome. Further studies will provide more explanations regarding the pathogenesis of SV, as well as allow the development of new focused therapies. In this regard, familial SV could offer a useful model for study.

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