Review

Genetic impact of pathogenesis and prognosis of ANCA-associated vasculitides

S. Borgmann[1], M. Haubitz[2]

[1]*Department of Medical Microbiology, University of Tübingen;* [2]*Department of Nephrology, Medical School, Hannover, Germany.*

Stefan Borgmann, MD; Marion Haubitz, MD.

Please address correspondence to: Stefan Borgmann, MD, Department of Medical Microbiology, University of Tübingen, Elfriede-Aulhorn-Strasse 6, D-72076 Tübingen, Germany.
E-mail: stefan.borgmann@med.uni-tuebingen.de

Received on March 12, 2004; accepted in revised form on September 3, 2004.

Clin Exp Rheumatol 2004; 22 (Suppl. 36): S79-S86.

Key words: ANCA, vasculitis, proteinase 3, myeloperoxidase, genetic associations.

ABSTRACT

Wegener's granulomatosis (WG), microscopic polyangiitis (MPA) and the Churg-Strauss syndrome (CSS) are small vessel vasculitides associated with anti-neutrophil cytoplasmic antibodies (ANCA). Cytoplasmic (c)-ANCA mainly target proteinase 3 (PR3) and are often observed in WG patients, while perinuclear (p)-ANCA predominantly bind to myeloperoxidase (MPO) and are common in patients with MPA and CSS.

It is suspected that a genetic background contributes to disease formation since the diseases are more prevalent in Caucasian populations. This article provides a detailed review of the genetic impact of the pathogenesis and prognosis of ANCA-associated vasculitides.

*Alpha-1 anti-trypsin is the physiological inhibitor of PR3 and carriage of the defective allele PI*Z was observed as the first genetic risk factor for the development of PR3-ANCA-associated vasculitis. Expression analyses have revealed that PR3 surface expression is genetically determined. Elevated levels of PR3 expression have been observed in WG patients and high levels of PR3 expression corresponded to increased risk of disease relapses. Furthermore, the non-carriage of CTLA-4 allele 86 was associated with WG formation, while homocygotic carriage of the CCR5 allele delta 32 seemed to prevent ANCA-negative WG. MPO-ANCA vasculitides were associated with certain alleles of CD18 polymorphisms. Lack of or only weak allelic associations of ANCA-vasculitides with polymorphic cytokine, HLA, and Fcγ receptor genes have been shown. Although, in practice, it is sometimes difficult to differentiate between WG and MPA, the diseases appear to be based on different genetic backgrounds.*

Introduction

Inflammation of blood vessels can occur either in conjunction with diseases of various origins such as infections, tumours, collagenoses and autoimmune diseases, or as primary vasculitic entities. As a consequence of a variety of overlapping clinical symptoms and histological findings, the primary vasculitides were often especially difficult to differentiate between, and various nomenclatures have been used over the past decades. Therefore, in 1994 the Chapel Hill conference developed disease definitions, facilitating the separation of the primary vasculitides (1). This scheme differentiates between diseases on the basis of the size of the affected vessels and includes large vessels (Takayasu arteritis, giant cell arteritis), medium-sized vessels (Polyarteritis nodosa, Kawasaki disease) and small vessels. Concerning the latter, anti-neutrophil cytoplasmic antibodies (ANCA) are a feature of Wegener's granulomatosis (WG), microscopic polyangiitis (MPA) and Churg-Strauss syndrome (CSS).

Anti-neutrophil cytoplasmic antibodies are closely associated with WG, MPA and CSS and their levels tend to increase in parallel with the degree of clinical disease activity (2-5). Myeloperoxidase (MPO)-ANCA predominantly result in perinuclear staining of alcohol-fixed neutrophils (p-ANCA) and are often present in patients suffering from MPA and CSS. In contrast, ANCA against proteinase 3 (PR3) mostly result in cytoplasmic staining (c-ANCA), as observed in WG patients (6-8).

Although reports of the familial occurrence of ANCA-associated vasculitides are relatively rare (9-16), the genetic background of small vessel vasculitides has been discussed. This idea is based on the observation that the dis-

eases predominantly affect Caucasian populations (17), and various studies have been performed analysing the genetic predispositions for the formation of ANCA-associated vasculitides. As will be detailed later, the results of these studies have demonstrated that PR3-ANCA- and MPO-ANCA-associated vasculitides, although often demonstrating similar clinical symptoms, appear to be based on distinct genetic predispostions.

When, in 1985, ANCA were initially described as specific serological markers of WG (18), it was unclear whether they actually contributed to disease formation or whether the finding of ANCA only represented an epiphenomenon. Today it is widely accepted that ANCA can activate primed neutrophils and also monocytes. Primed leukocytes demonstrate an increased number of adhesion molecules and large amounts of cytokine release, resulting in enhanced endothelial adhesion. Finally, activation by ANCA binding leads to a respiratory burst with the release of toxic leukocyte products, especially proteases (MPO, elastase, cathepsins, PR3) and radicals (H_2O_2, O_2-), resulting in the necrosis of the respective blood vessels. In agreement with this model, highly elevated numbers of circulating necrotic endothelial cells were demonstrated in patients with ANCA-associated vasculitis (19).

According to this pathogenetic concept, genetic analyses were focussed on gene polymorphisms of ANCA target antigens, cytokines and adhesion molecules. Furthermore, possible associations of HLA alleles were intensively examined and the first association discovered was that of WG with PI*Z allele of α1-antitrypsin.

*PI*Z defective allele of α1-antitrypsin*

Homozygosity of the defective PI*Z allele of α1-antitrypsin (proteinase inhibitor, PI), which results in decreased levels of PI, is associated with the development of emphysema in almost all adults and with liver cirrhosis in 25% of children (20). PI inactivates various proteases and is the most important inhibitor of PR3 in the circulation. Interestingly, carrier frequency of the PI*Z allele is 100-fold increased in patients with WG. Therefore, approximately 5% of those patients are carriers of the PI*Z allele, most of them as heterozygous phenotype (21-23). Based on this increased frequency, it was assumed that a disturbed protease/protease inhibitor balance contributes to disease formation and also to severe and extended organ manifestations with poor clinical outcome (24, 25). On the other hand, a PI*Z defective allele frequency of 5% indicates that most WG patients suffer from disease without carrying a defective allele. Furthermore, the carriage of PI*Z defective allele in a random population did not result in an increased frequency of WG (26,27). These observations excluded the presence of the PI*Z allele as a major risk factor in the formation of disease.

The PI gene is part of a cluster of structurally related serine protease inhibitor genes (serpins) located at chromosome 14q32.1 (28,29) and it has been suspected that an unidentified protein, encoded by one of these genes, contributes to disease formation. Haplotype analysis of this gene cluster has demonstrated strong allelic linkages in PR3-ANCA vasculitis patients (30). Allelic linkages were also observed in healthy controls and in MPO-ANCA vasculitis patients. However, these associations extended between gene loci other than those of PR3-ANCAvasculitis patients and were comparably weak (30, 31). These findings support the hypothesis that an unidentified target protein with a gene located near the Pl gene locus contributes to PR3-ANCA-associated vasculitis.

Based on the finding that ANCA-associated vasculitides are markedly less frequent in non-Caucasian populations, genetic associations were predominantly performed on Caucasians. No differences were observed between the WG patients and controls when PI*Z allele frequency was analysed in a Chinese population (32), emphasising the likely presence of an unidentified factor contributing to disease formation.

ANCA target proteins

The main target protein of c-ANCA is PR3. In resting PMN, most PR3 is stored intracellularly within the acurophilic granules and also in a second compartment of secretory vesicles (8, 33). Following the priming of PMN, intracellular PR3 is transferred to the cellular membrane, allowing binding of PR3-ANCAand subsequent PMN activation. Finally, PR3 is released into the extracellular environment along with other proteases and respiratory burst products (34), resulting in detrimental vessel damage. A minor part of PR3 is located in the cell membrane of resting PMN and the amount of membranous PR3 appears important for c-ANCA-associated vasculitis formation. This hypothesis is based on the observation that constitutive PR3 membrane expression is individually determined (35) and that the percentage of resting PMN demonstrating PR3 surface expression varies as do the PR3 surface densities of these PMN (36, 37). Importantly, elevated levels of PR3 expression were observed in WG patients and high levels of PR3 expression corresponded to an increased risk of disease relapses (36). Measurement of PR3 expression in resting PMN from monozygotic and dizygotic twins underlined the fact that PR3 surface expression is genetically determined (37).

Genetic analyses of the entire PR3 gene revealed various polymorphic regions. Among others, the promoter region showed several polymorphisms, of which the G allele of an A-564G substitution was associated with WG. The G allele represents a GC-box element contributing to Sp1 transcription factor binding and the A allele is a CACCC transcription factor binding site (38). It is therefore highly likely that this polymorphism contributes to PR3 expression rates. However, since the amount of intracellular PR3 was not correlated with PR3 surface expression (37), it remains unclear whether PR3 promoter polymorphism alleles determine total cellular PR3 and also PR3 surface expression of resting PMN.

The interesting results concerning PR3 expression raise the question whether MPO gene polymorphisms also facilitate the formation of MPO-ANCA-associated vasculitis. This supposition is

underlined by the finding that MPO-ANCA-mediated induction of respiratory burst and protease release does not occur in leukocytes from MPO-deficient individuals (39). In the MPO promoter region a G-463A polymorphism resulted in the substitution of guanine by adenine. Carriage of the less frequent A allele led to reduced activity of MPO and decreased the risk of lung cancer (40). Based on these observations, A allele frequency was suspected to be low in MPO-ANCA-associated vasculitis patients. However, when G-463A MPO polymorphism was analysed in such patients, allelic frequencies were not significantly different from those of healthy controls and PR3-ANCA-associated vasculitis patients (41,42). On the other hand, A allele frequency was lower in female patients suffering from MPO-ANCA-associated-vasculitis, while a higher A allele frequency was demonstrated in MPO-ANCA-associated vasculitis patients presenting with shorter relapse-free periods and with frequent ear-nose-throat affections (41). As these findings were not confirmed by others (42), it remains doubtful that MPO G-463A promoter polymorphism is associated with the formation of MPO-ANCA-associated vasculitis in females or with clinical manifestations.

Beside MPO, various other proteins including azurocidin and neutrophil elastase (43-46) have been found to act as p-ANCA targets. Intronic polymorphisms were discovered within the genes for azurocidin and neutrophil elastase, however, allelic frequencies were similar in healthy controls, PR3-ANCA- and MPO-ANCA-associated vasculitis patients. Therefore, these polymorphisms were excluded as risk factors of ANCA-associated vasculitides (47).

Adhesion molecules

The adhesion of leukocytes to the endothelial vessel wall is a pivotal step in the pathogenesis of vasculitis. By inducing up-regulation of adhesion molecules in leukocytes (48,49) and endothelial cells (50), ANCAhave been described to facilitate the adhesion of PMN to blood vessels (51). While polymorph regions within the CD11, ICAM-1 and E-selectin genes were not associated with ANCA-associated vasculitides, allelic coupling was observed between polymorphic regions in the CD18 gene and MPO-ANCA vasculitis, but not with PR3-ANCA vasculitis (52, 53). As these alleles display “silent polymorphisms”, the mechanism(s) by which formation of MPO-ANCA vasculitides is mediated remains unclear. One polymorph region, however, is located within one of the multiple CD18 transcription initiation sites and, therefore, increased expression of CD18 in leukocytes might contribute to the formation of MPO-ANCAvasculitis.

HLA and co-stimulatory molecules

Beside the fact that PMN play a major role in blood vessel destruction, various findings indicate that T cells are also important for the development of ANCA-associated vasculitis.

This is indicated by the fact that serum levels of soluble CD25 (α-chain of IL-2-receptor) correlated with WG disease activity (54,55). High numbers of CD-4+ T cells were demonstrated in kidney biopsies taken from WG patients with necrotising glomerulonephritis (56, 57), and it was recently observed that T cells are involved in the formation of vasculitic lesions (58). Moreover, clonal expansion of T cells was observed in WG patients (59, 60) and these cells were predominantly effector-memory cells (58,61). Although various other reports underline the importance of T cells in vasculitis formation (62-66), it has not been finally resolved whether T cell help is essential for ANCAproduction of B cells or not (67). T cells are stimulated by T cell receptor activation via binding to a specific peptide within HLA molecules. Since HLA class II molecules comprise a highly variable group and associations with other autoimmune diseases have been found; several studies have focussed on allelic HLA associations with ANCA-associated vasculitides. A summary of selected studies in Table I reveals mainly different results (68-79), indicating at best a weak coupling of ANCA-associated vasculitides with the HLAphenotype.

In two studies DR6 subtype allele DRB1*13 frequency was decreased in patients suffering from ANCA-associated vasculitides (75, 78) and it was speculated that DRB1*13 under-representation, which might lower the ability to prevent bacterial infections, contributes to increased colonisation with *Staphylococcus aureus* (80), as observed in WG patients (81). Recently, the association of WG with HLA-DPB1*-0401 allele was described (79). Interestingly, the authors also observed that an extended haplotype comprising HLA-DPB1*0401 and RXRX03 (retinoid X receptor b allele 3) alleles was even more strongly associated with WG. This finding raises the question whether other HLA-linked genes might also encode proteins that contribute to disease formation. In a study investigating Japanese patients, an association of HLA-DRB1*0901 with MPO-ANCA-associated vasculitides was observed (82). These results differ from those obtained in Caucasian patients and remain to be confirmed.

Beside T cell receptor stimulation via HLA-antigen complex binding, naïve T cells require a second signal mediated by co-stimulatory molecules. The most important activating molecule is CD28, which binds to CD80 and CD86 present on antigen-presenting cells. At later periods of T cell responses CD28 is down-regulated, while CTLA-4 increasingly occurs at the surface of the T cells. CTLA-4 also binds to CD80 and CD86; however, unlike CD28, CTLA-4 binding mediates a negative signal which down-regulates T cell activation. Various mechanisms have been discussed by which T cell activation is prevented or terminated (83): prevention of CD28 signalling by competition with the shared receptors (CD80 and CD86), triggering of inhibitory signals that interfere with T cell receptor signalling, and release of inhibitory factors by regulatory T cells upon CTLA-4 ligation. Furthermore, CTLA-4 signalling was able to prevent antigen-induced cell death in a T cell hybridoma cell line (84).

Based on this finding it was discussed that CTLA-4, beside its inhibitory function in naïve T cells, might also be involved in the control of memory T cell survival and also in the regulatory

capacity of CD4+ CD25+ T cells. The impact of CTLA-4 on the function of differentiated T cells is underlined by the finding that memory T cells had high amounts of intracellular stored CTLA-4, while naïve T cells only possessed a small intracellular reservoir. In contrast to naïve T cells that showed only transient surface expression upon stimulation, memory and also CD4+ CD25+ regulatory T cells showed sustained surface expression for at least 24 hours (85). These findings suggest CTLA-4 as a candidate gene of autoimmune disease formation, and recently the association with Graves' disease and type 1 diabetes mellitus was described (86).

Three polymorphisms within the CTLA-4 gene were analysed in WG patients. The first polymorphism was a C/T substitution at position -318 within the promoter region. In WG patients homozygosity of the C allele was decreased and the frequency of the T/C genotype was increased (87). However, this base pair exchange did not result in the alteration of any known consensus sequence and therefore the pathogenic relevance of this finding is unclear. The second polymorphism was an A/G polymorphism at position +49 resulting in an amino-acid substitution from Thr to Ala within the leading sequence. The third polymorphism was an (AT)n microsatellite polymorphism at position 642 of the 3' untranslated region of exon 3. The frequency of the shortest allele 86 of the third polymorphism was decreased in WG patients (88) and, furthermore, this allele was not linked to the A allele of the second polymorphism, as was shown in controls. The G allele of the second polymorphism, and also those alleles of the second polymorphism longer than 84 bp, mediated a decreased inhibitory function of CTLA-4 (89, 90), which may contribute to differences in CTLA-4 levels and T cell activation in vasculitis patients compared to controls. Moreover, serum levels of soluble CD25 correlated with the number of AT repeats, indicating that this polymorphism has an impact on T cell activation mechanisms (89).

Interestingly, the expression of CTLA-4 on the surface of non-activated peripheral T cells was low in controls and high in WG patients, indicating that the T cells of WG patients were in an activated state. In agreement with this result, CTLA-4 expression levels of the T cells of WG patients correlated with disease activity. Upon mitogen stimulation, however, T cells from WG patients showed lower CTLA-4 levels, suggesting an imbalance of the intracellular stimulatory and inhibitory signalling pathways (91). The impact of CTLA-4 polymorphisms on WG was also recently discussed by Day *et al.* (92).

Table I. Selected studies analysing associations of HLAclass II alleles with ANCA-associated vasculitides.

Reference	(n)	Diagnosis	Method	Association
Strimlan *et al*. (68)	31	WG	Serol.	-
Katz *et al*. (69)	31	WG	Serol.	B8↑
Elkon *et al*. (70)	46	WG,PAN,CSS	Serol.	DR2↑ (WG)
Murty *et al*. (71)	41	WG	RFLP	-
Papiha *et al*. (72)	27	WG	Serol.	DR1↑
Spencer *et al*. (73)	59	WG, MPA	RFLP, SSO	DQw7↑, DR3↓
Thomson *et al*. (74)	27	WG, MPA, RA	Serol.	DR8↑
Hagen *et al*. (75)	224	WG, MPA	Serol.	DR6-DRB1*13↓
Zhang *et al*. (76)	94	WG, MPA, RLV	RFLP, SSO	-
Boki *et al*. (77)	66	WG; MPA; CSS	MIC; RDBT	DR1↑ (WG)
Gencik *et al*. (78)	101	WG, MPA	RFLP, SSO	DR6-DRB1*13↓ DR4↑ (WG*)
Jagiello *et al*. (79)	150	WG	RFLP	DPB1*0401↑

n: number of patients; WG: Wegener's granulomatosis; PAN: polyarteriitis nodosa; CSS: Churg-Strauss syndrome; MPA: microscopic polyangiitis; RA: rheumatoid arthritis; RLV: renal limited vasculitis; WG*: Wegener's granulomatosis with end-stage renal disease; Serol: serologic typing; RFLP: restriction fragment length polymorphism typing; SSO: sequence-specific oligonucleotide typing; MIC: microlymphocytotoxicity method; RDBT: reverse dot blot technique; ↑: increased frequency; ↓: decreased frequency.

Cytokines, chemokines and their receptors

Early analyses of the genetic background of ANCA-associated vasculitis focussed on cytokines, since they contribute to inflammatory processes. *In vitro*, TNF-α and IL-8 lead to a translocation of PR3 from azurophil granules to the cell surface (93) and this is essential for c-ANCA binding to PR3. On the other hand, incubation of PMN with anti-PR3- and anti-MPO-ANCA induces the release of IL-1β from the PMN (94) and anti-PR3-ANCA mediated IL-8 release from primed monocytes (95). TNF-α, IL-1β and IL-2 receptors were observed in kidney biopsies taken from ANCA-associated vasculitis patients and the number of cytokine-expressing cells was markedly increased in patients with active lesions (96). Moreover, elevated levels of soluble TNF-receptors were found in ANCA-positive sera (97).

Allelic analyses of a TGF-β polymorphism revealed no frequency differences between WG patients and healthy controls and, also, the frequency of homocygotic persons was similar in the two groups. In contrast to this finding, the frequency of homocygotic patients was increased in WG patients carrying the A allele of a G-1082A polymorphism within the IL-10 promoter (98). The A allele of this promoter polymorphism resulted in decreased secretion rates (99) of IL-10, therefore reduced levels of this anti-inflammatory cytokine might facilitate the formation of WG.

In an extensive genetic examination of c-ANCA and p-ANCA patients, no allelic linkages of various polymorphic regions within the genes of TNF-α, IL-2, IL-5 receptor α were observed (78). Parts of these results were confirmed at a later stage when TNF-α 308 promoter polymorphism was examined. Furthermore, no allelic association of a polymorphism within the IL-1β exon 5

was detected (86). While *in vitro* analyses showed that allele 2 of this exonic polymorphism resulted in increased production of IL-1β, allele 2 of a polymorphism within intron 2 of the IL-1 receptor antagonist gene led to increased production of the physiological IL-1β inhibitor. Based on these observations, it was discussed that the combination of the presence of IL-1β allele 2 and the absence of an IL-1 receptor antagonist allele 2 form a pro-inflammatory genotype. However, neither this nor any other allelic combination appeared to contribute to disease formation. Interestingly, this pro-inflammatory genotype was increased in PR3-ANCA patients upon dialysis, but not in MPO-ANCAdialysis patients. Therefore, genetic determination of an IL-1β and IL-1 receptor antagonist imbalance might aggravate the clinical courses of PR3-ANCA-associated vasculitides (100).

Members of the CC-chemokine subfamily (RANTES, MIP-1α, MIP-1β) attract chemokine receptor CCR5-expressing leukocytes. These leukocytes are macrophages, dendritic cells and T lymphocytes displaying a Th1 phenotype. CCR5-expressing leukocytes were found in the upper airway lesions of WG patients and CCR5+ cells were enriched in patients with localized WG as compared to those in patients with generalized WG. Most of CCR5 receptor-expressing CD4+ T cells within these lesion cells lacked CD28, and therefore these cells were discussed as late differentiated memory T cells mediating Th1 responses (101). Although the percentage of natural killer cells expressing CCR5 receptors, isolated from peripheral blood, was similar in controls and patients with inactive WG, it was increased in patients suffering from generalized WG (102). Allelic frequencies of two polymorphisms within the RANTES gene, influencing protein expression, were similar in WG patients and in healthy controls; this excluded a strong impact of certain RANTES alleles on WG formation (103).

A 32 bp region within the CCR5 gene may be deleted (Δ32) resulting in a non-functional protein. Presence of the Δ32 truncated allele reduced susceptibility to HIV infection and was also associated with benign courses of autoimmune diseases (reviewed in 103). Interestingly, homozygosity for CCR-$5^{\Delta 32/\Delta 32}$ allele seemed to protect against the development of rheumatoid arthritis (104). However, in a group of 114 WG patients, allelic frequency of the Δ32 allele was similar to those of healthy controls (103). Of these WG patients, almost 80% showed circulating ANCA. In this group of 89 ANCA-positive patients, the frequency of CCR5 allele Δ32 was in the normal range of approximately 20%, whereas none of the 25 WG patients lacking circulating ANCA displayed the CCR5 allele Δ32. Therefore, CCR5 Δ32 carriage might have a protective role in a subset of patients.

Fcγ receptors

When ANCA bind to their antigen on the cell surface, binding of Fc-fragments by Fcγ-receptors contribute to PMN activation (reviewed in 105). As Fcγ-receptors display a highly polymorphic family of molecules, analyses have focussed on polymorphic alleles of various groups (FcγRIIa, FcγRIIIa, FcγRIIIb). However, most of these analyses have failed to show allelic coupling with ANCA-associated vasculitides (78, 106-108). The only association that has been demonstrated was homozygosity of the NA1 allele of a bi-allelic FcγRIIIb polymorphism in the group of MPO-ANCA patients (107). However, allelic frequencies of both alleles (NA1 and NA2) were similar in MPO-ANCA patients, PR3-ANCA patients and in controls. Therefore, the importance of the FcγRIIIb NA1 allele seems doubtful. When WG patients were homozygotic carriers of both the R131 allele of the FcγRIIa polymorphism and the F158 allele of the FcγRIIa polymorphism, an increased incidence of relapses was observed; possibly due to a decreased ability to eliminate *S. aureus* (106).

Other proteins

Allelic coupling between various other immunologically relevant gene polymorphisms and ANCA-associated vasculitides were analysed. Although direct involvement of complement activation in the pathogenesis of small vessel vasculitides could not be shown (109), association of the complement allele C4A3 with ANCA-associated vasculitides was demonstrated. Furthermore, F allele of a bi-allelic C3 polymorphism was also associated with WG (110). The impact of these allelic couplings remains to be elucidated, especially since no functional differences between the two alleles of the C3 polymorphism were found.

No association was detected between a bi-allelic polymorphism within the angiotensin-converting enzyme gene in intron 16 and WG (97).

Conclusion

Various studies have been performed to analyse a possible genetic background in ANCA-associated vasculitides. Although some genetic associations have been demonstrated, none of these sufficiently explain the formation of these diseases. Therefore, among other important factors (i.e. infections, environment, exposition to silicate) genetic predisposition might contribute to the susceptibility and formation of ANCA-associated vasculitides.

References

1. JENNETTE JC, FALK RJ, ANDRASSY K *et al.*: Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum* 1994; 37: 187-92.
2. GASKIN G, SAVAGE CO, RYAN JJ, JONES S, REES AJ, LOCKWOOD CM *et al.*: Anti-neutrophil cytoplasmic antibodies and disease activity during long-term follow-up of 70 patients with systemic vasculitis. *Nephrol Dial Transplant* 1991; 6: 689-94.
3. WIIK A: Autoantibodies in vasculitis. *Arthritis Res Ther* 2003; 5: 147-52.
4. SCHMITT WH, VAN DER WOUDE FJ: Clinical applications of antineutrophil cytoplasmic antibody testing. *Curr Opin Rheumatol* 2004; 16: 9-17.
5. HOFFMAN GS, SPECKS U: Antineutrophil cytoplasmic antibodies. *Arthritis Rheum* 1998; 41: 1521-37
6. LESAVRE P: The diagnostic and prognostic significance of ANCA. *Ren Fail* 1996; 18: 803-12.
7. HAUSCHILD S, SCHMITT WH, CSERNOK E, FLESCH BK, RAUTMANN A, GROSS WL: ANCA in systemic vasculitides, collagen vascular diseases, rheumatic disorders and inflammatory bowel diseases. *Adv Exp Med Biol* 1993; 336: 245-51.
8. CSERNOK E, LUDEMANN J, GROSS WL, BAINTON DF: Ultrastructural localization of proteinase 3, the target antigen of anti-cy-

toplasmic antibodies circulating in Wegener's granulomatosis. *Am J Pathol* 1990; 137: 1113-20.
9. HULL CM, COUSER WG, KNOSTMAN JD: A familial case of P-ANCAglomerulonephritis presenting in a father and daughter. *Am J Kidney Dis* 2000;35: E23.
10. BRENER Z, COHEN L, GOLDBERG SJ, KAUFMAN AM: ANCA-associated vasculitis in Greek siblings with chronic exposure to silica. *Am J Kidney Dis* 2001; 38: E28.
11. STONEY PJ, DAVIES W, HO SF, PATERSON IC, GRIFFITH IP: Wegener's granulomatosis in two siblings: a family study. *J Laryngol Otol* 1991; 105: 123-4.
12. HAY EM, BEAMAN M, RALSTON AJ, ACKRILL P, BERNSTEIN RM, HOLT PJ: Wegener's granulomatosis occurring in siblings. *Br J Rheumatol* 1991; 30: 144-5.
13. NOWACK R, LEHMANN H, FLORES-SUAREZ LF, NANHOU A, VAN DER WOUDE FJ: Familial occurrence of systemic vasculitis and rapidly progressive glomerulonephritis. *Am J Kidney Dis* 1999; 34: 364-73.
14. MURPHY EA, STURROCK RD, FOX JG, BOULTON-JONES JM: Two sisters with ANCA positive vasculitis. *Ann Rheum Dis* 1993; 52: 385.
15. MANGANELLI P, GIACOSA R, FIETTA P, ZANETTI A, NERI TM: Familial vasculitides: Churg-Strauss syndrome and Wegener's granulomatosis in 2 first-degree relatives. *J Rheumatol* 2003; 30: 618-21.
16. FIETTA P: Systemic vasculitides: immunogenetics and familial clustering. *Clin Exp Rheumatol* 2004; 22: 238-51.
17. HOFFMAN GS, KERR GS, LEAVITT RY *et al*.: Wegener granulomatosis: an analysis of 158 patients. *Ann Intern Med* 1992; 116: 488-98.
18. VAN DER WOUDE FJ, RASMUSSEN N, LOBATTO S *et al*.: Autoantibodies against neutrophils and monocytes: tool for diagnosis and marker of disease activity in Wegener's granulomatosis. *Lancet* 1985; 1: 425-9.
19. WOYWODT A, STREIBER F, DE GROOT K, REGELSBERGER H, HALLER H, HAUBITZ M: Circulating endothelial cells as markers for ANCA-associated small-vessel vasculitis. *Lancet* 2003; 361: 206-10.
20. KALSHEKER NA: Molecular pathology of alpha 1-antitrypsin deficiency and its significance to clinical medicine. *QJM* 1994; 87: 653-8.
21. ESNAULT VL, TESTA A, AUDRAIN M *et al*.: Alpha 1-antitrypsin genetic polymorphism in ANCA-positive systemic vasculitis. *Kidney Int* 1993; 43: 1329-32.
22. 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: 543-8.
23. MAZODIER P, ELZOUKI AN, SEGELMARK M, ERIKSSON S: Systemic necrotizing vasculitides in severe alpha1-antitrypsin deficiency. *QJM* 1994; 89: 599-611.
24. 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: 844-50.
25. 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; 4: 206-13.
26. LHOTTA K, VOGEL W, MEISL T *et al*.: Alpha 1-antitrypsin phenotypes in patients with anti-neutrophil cytoplasmic antibody-positive vasculitis. *Clin Sci* 1994; 87: 693-5.
27. AUDRAIN MA, SESBOUE R, BARANGER TA *et al*.: Analysis of anti-neutrophil cytoplasmic antibodies (ANCA): frequency and specificity in a sample of 191 homozygous (PiZZ) alpha1-antitrypsin-deficient subjects. *Nephrol Dial Transplant* 2001; 16: 39-44.
28. BILLINGSLEY GD, WALTER MA, HAMMOND GL, COX DW: Physical mapping of four serpin genes: alpha 1-antitrypsin, alpha 1-antichymotrypsin, corticosteroid-binding globulin, and protein C inhibitor, within a 280-kb region on chromosome I4q32.1. *Am J Hum Genet* 1993; 52: 343-53.
29. BYTH BC, BILLINGSLEY GD, COX DW: Physical and genetic mapping of the serpin gene cluster at 14q32.1: allelic association and a unique haplotype associated with alpha 1-antitrypsin deficiency. *Am J Hum Genet* 1994; 55: 126-33.
30. BORGMANN S, ENDISCH G, URBAN S, SITTER T, FRICKE H: 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: 244-8.
31. BORGMANN S, HAUBITZ M, SCHWAB SG: Lack of association of alpha-1 antichymotrypsin gene polymorphism with PR3-ANCAand MPO-ANCAassociated vasculitis. *Autoimmunity* 2002; 35: 435-9.
32. LEE SS, LAWTON JW, KO KH: Alpha1 antitrypsin phenotypic variability is not associated with ANCAin southern Chinese. *Ann Rheum Dis* 2001; 60: 725-6.
33. 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: 2487-96.
34. BAGGIOLINI M, SCHNYDER J, BRETZ U, DEWALD B, RUCH W: Cellular mechanisms of proteinase release from inflammatory cells and the degradation of extracellular proteins. *Ciba Found Symp* 1979; 75: 105-21.
35. 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: 1224-33.
36. ROROK AA, STEGEMAN CA, LIMBURG PC, KALLENBERG CG: Neutrophil membrane expression of proteinase 3 (PR3) is related to relapse in PR3-ANCA-associated vasculitis. *J Am Soc Nephrol* 2002; 13: 2232-8.
37. SCHREIBER A, BUSJAHN A, LUFT FC, KETTRITZ R: Membrane expression of proteinase 3 is genetically determined. *J Am Soc Nephrol* 2003; 14: 68-75.
38. GENCIK M, MELLER S, BORGMANN S, FRICKE H: Proteinase 3 gene polymorphisms and Wegener's granulomatosis. *Kidney Int* 2000; 58: 2473-7.
39. REUMAUX D, DE BOER M, MEIJER AB, DUTHILLEUL P, ROOS D: Expression of myeloperoxidase (MPO) by neutrophils is necessary for their activation by anti-neutrophil cytoplasm autoantibodies (ANCA) against MPO. *J Leukoc Biol* 2003; 73: 841-9.
40. CASCORBI I, HENNING S, BROCKMOLLER J *et al*.: Substantially reduced risk of cancer of the aerodigestive tract in subjects with variant-463A of the myeloperoxidase gene. *Cancer Res* 2000; 60: 644-9.
41. REYNOLDS WF, STEGEMAN CA, COHEN 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: 154-60.
42. FIEBELER A, BORGMANN S, WOYWODTA, HALLER H, HAUBITZ M: No association of G-463A myeloperoxidase gene polymorphism with MPO-ANCA-associated vasculitis. *Nephrol Dial Transplant*, in press.
43. YANG JJ, TUTTLE R, FALK RJ, JENNETTE JC: Frequency of anti-bactericidal/permeability-increasing protein (BPI) and anti-azurocidin in patients with renal disease. *Clin Exp Immunol* 1996; 105: 125-31.
44. ZHAO MH, LOCKWOOD CM: Azurocidin is a novel antigen for anti-neutrophil cytoplasmic autoantibodies (ANCA) in systemic vasculitis. *Clin Exp Immunol* 1996; 103: 397-402.
45. ODA T, HOTTA O, TAGUMA Y, KITAMURAH, SUDO K, HORIGOME I, CHIBAS, YOSHIZAWA N, NAGURA H: Involvement of neutrophil elastase in crescentic glomerulonephritis. *Hum Pathol* 1997; 28: 720-8.
46. MORCOS M, ZIMMERMANN F, RADSAK M, WORNER I, KRAMER MD, ROLAND J, HANSCH GM, ANDRASSY K: Autoantibodies to polymorphonuclear neutrophil elastase do not inhibit but enhance elastase activity. *Am J Kidney Dis* 1998; 31: 978-85.
47. BORGMANN S, FRICKE-H: No association between novel polymorphisms of heparin binding globulin (HBP, acurocidin) and of neutrophil elastase (ELA2) genes and ANCA associated vasculitides. *Nieren- und Hochdruckkrankheiten* 2002; 12: 561-65.
48. JOHNSON PA, ALEXANDER HD, MCMILLAN SA, MAXWELL AP: Up-regulation of the endothelial cell adhesion molecule intercellular adhesion molecule-1 (ICAM-1) by autoantibodies in autoimmune vasculitis. *Clin Exp Immunol* 1997; 108: 234-42.
49. JOHNSON PA, ALEXANDER HD, MCMILLAN SA, MAXWELLAP: Up-regulation of the granulocyte adhesion molecule Mac-1 by autoantibodies in autoimmune vasculitis. *Clin Exp Immunol* 1997; 107: 513-9.
50. MAYET WJ, SCHWARTING A, ORTH T, DUCHMANN R, MEYER ZUM BUSCHENFELDE KH: Antibodies to proteinase 3 mediate expression of vascular cell adhesion molecule-1 (VCAM-1). *Clin Exp Immunol* 1996; 103: 259-67.
51. MAYET WJ, MEYER ZUM BUSCHENFELDE KH: Antibodies to proteinase 3 increase adhesion of neutrophils to human endothelial

cells. *Clin Exp Immunol* 1993; 94: 440-6.
52. GENCIK M, MELLER S, BORGMANN S *et al.*: *et al*.: The association of CD18 alleles with anti-myeloperoxidase subtypes of ANCA-associated systemic vasculitides. *Clin Immunol* 2000; 94: 9-12.
53. 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: 269-72.
54. SCHMITT WH, HEESEN C, CSERNOK E, RAUTMANN A, GROSS WL: Elevated serum levels of soluble interleukin-2 receptor in patients with Wegener's granulomatosis. Association with disease activity. *Arthritis Rheum* 1992; 35: 1088-96.
55. STEGEMAN CA, TERVAERT JW, HUITEMA MG, KALLENBERG CG: Serum markers of T cell activation in relapses of Wegener's granulomatosis. *Clin Exp Immunol* 1993; 91: 415-20.
56. BOLTON WK, INNES DJ JR, STURGILL BC, KAISER DL: T-cells and macrophages in rapidly progressive glomerulonephritis: clinicopathologic correlations. *Kidney Int* 1987; 32: 869-76.
57. MULLER GA, MULLER CA, MARKOVIC-LIPKOVSKI J, KILPER RB, RISLER T: Renal major histocompatibility complex antigens and cellular components in rapidly progressive glomerulonephritis identified by monoclonal antibodies. *Nephron* 1988; 49: 132-9.
58. VOGT S, IKING-KONERT C, HUG F, ANDRASSY K, HANSCH GM: Shortening of telomeres: Evidence for replicative senescence of T cells derived from patients with Wegener's granulomatosis. *Kidney Int* 2003; 63: 2144-51.
59. GISCOMBE R, GRUNEWALD J, NITYANAND S, LEFVERT AK: T cell receptor (TCR) V gene usage in patients with systemic necrotizing vasculitis. *Clin Exp Immunol* 1995; 101: 213-9.
60. GRUNEWALD J, HALAPI E, WAHLSTROM J *et al.*: T-cell expansions with conserved T-cell receptor beta chain motifs in the peripheral blood of HLA-DRB1*0401 positive patients with necrotizing vasculitis. *Blood* 1998; 92: 3737-44.
61. LAMPRECHT P, MUELLER A, GROSS WL: CD28- T cells display features of effector memory T cells in Wegener's granulomatosis. *Kidney Int* 2004; 65: 1113.
62. BALLIEUX BE, VAN DER BURG SH, HAGEN EC, VAN DER WOUDE FJ, MELIEF CJ, DAHA MR: Cell-mediated autoimmunity in patients with Wegener's granulomatosis (WG) *Clin Exp Immunol* 1995; 100: 186-93.
63. BROUWER E, STEGEMAN CA, HUITEMA MG, LIMBURG PC, KALLENBERG CG: T cell reactivity to proteinase 3 and myeloperoxidase in patients with Wegener's granulomatosis (WG). *Clin Exp Immunol* 1994; 98: 448-53.
64. LOCKWOOD CM, THIRU S, STEWART S *et al.*: Treatment of refractory Wegener's granulomatosis with humanized monoclonal antibodies. *QJM* 1996; 89: 903-12.
65. KOMOCSI A, LAMPRECHT P, CSERNOK E *et al.*: Peripheral blood and granuloma CD-4(+)CD28(-) T cells are a major source of interferon-gamma and tumor necrosis factor-alpha in Wegener's granulomatosis. *Am J Pathol* 2002; 160: 1717-24.
66. WINEK J, MUELLER A, CSERNOK E, GROSS WL, LAMPRECHT P: Frequency of proteinase 3 (PR3)-specific autoreactive T cells determined by cytokine flow cytometry in Wegener's granulomatosis. *J Autoimmun* 2004; 22: 79-85.
67. CLAYTON AR, SAVAGE CO: Production of antineutrophil cytoplasm antibodies derived from circulating B cells in patients with systemic vasculitis. *Clin Exp Immunol* 2003; 132: 174-9.
68. STRIMLAN CV, TASWELL HF, KUEPPERS F, DEREMEE RA, MCDONALD TJ: HLA-A antigens of patients with Wegener's granulomatosis. *Tissue Antigens* 1978; 11: 129-31.
69. KATZ P, ALLING DW, HAYNES BF, FAUCI AS: Association of Wegener's granulomatosis with HLA-B8. *Clin Immunol Immunopathol* 1979; 14: 268-70.
70. ELKON KB, SUTHERLAND DC, REES AJ, HUGHES GR, BATCHELOR JR: HLA antigen frequencies in systemic vasculitis: increase in HLA-DR2 in Wegener's granulomatosis. *Arthritis Rheum* 1983; 26: 102-5.
71. MURTY GE, MAINS BT, MIDDLETON D, MAXWELL AP, SAVAGE DA: HLA antigen frequencies and Wegener's granulomatosis. *Clin Otolaryngol* 1991; 16: 448-51.
72. PAPIHA SS, MURTY GE, AD'HIA A, MAINS BT, VENNING M: Association of Wegener's granulomatosis with HLAantigens and other genetic markers. *Ann Rheum Dis* 1992; 51: 246-8.
73. SPENCER SJ, BURNS A, GASKIN G, PUSEY CD, REES AJ: HLA class II specificities in vasculitis with antibodies to neutrophil cytoplasmic antigens. *Kidney Int* 1992; 41: 1059-63.
74. THOMSON JB, HULSE D, GALBRAITH I, MCKAY IC, FIELD M: Autoantibody associations with MHC class II antigens in scleroderma and autoimmune vasculitis. *Autoimmunity* 1994; 19: 265-9.
75. HAGEN EC, STEGEMAN CA, D'AMARO J *et al.*: Decreased frequency of HLA-DR13-DR6 in Wegener's granulomatosis. *Kidney Int* 1995; 48: 801-5.
76. ZHANG L, JAYNE DR, ZHAO MH, LOCKWOOD CM, OLIVEIRA DB: Distribution of MHC class II alleles in primary systemic vasculitis. *Kidney Int* 1995; 47: 294-8.
77. BOKI KA, DAFNI U, KARPOUZAS GA, PAPASTERIADES C, DROSOS AA, MOUTSOPOULOS HM: Necrotizing vasculitis in Greece: clinical, immunological and imunogenetic aspects. A study of 66 patients. *Br J Rheumatol* 1997; 36: 1059-66.
78. GENCIK M, BORGMANN S, ZAHN R *et al.*: Immunogenetic risk factors for anti-neutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitis. *Clin Exp Immunol* 1999; 117: 412-7.
79. 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;114:468-77.
80. MITERSKI B, EPPLEN JT, GENCIK M: On the genetic contribution to selected multifactorial diseases with autoimmune characteristics. *Cell Mol Biol* 2002; 48: 331-41.
81. STEGEMAN CA, TERVAERT JW, SLUITER WJ, MANSON WL, DE JONG PE, KALLENBERG CG: Association of chronic nasal carriage of *Staphylococcus aureus* and higher relapse rates in Wegener granulomatosis. *Ann Intern Med* 1994; 120: 12-7.
82. TSUCHIYA N, KOBAYASHI S, KAWASAKI A *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: 1534-40.
83. SANSOM DM: CD28, CTLA-4 and their ligands: who does what and to whom? *Immunology* 2000; 101: 169-77.
84. DA ROCHA DIAS S, RUDD CE: CTLA-4 blockade of antigen-induced cell death. *Blood* 2001; 97: 1134-7.
85. JAGO CB, YATES J, CAMARA NO, LECHLER RI, LOMBARDI G: Differential expression of CTLA-4 among T cell subsets. *Clin Exp Immunol* 2004; 136: 463-71.
86. UEDA H, HOWSON JM, ESPOSITO L *et al.*: Association of the T-cell regulatory gene CTLA4 with susceptibility to autoimmune disease. *Nature* 2003; 423: 506-11.
87. 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: 950-3.
88. HUANG D, GISCOMBE R, ZHOU Y, LEFVERT AK: Polymorphisms in CTLA-4 but not tumor necrosis factor-alpha or interleukin 1beta genes are associated with Wegener's granulomatosis. *J Rheumatol* 2000; 27: 397-401.
89. HUANG D, GISCOMBE R, ZHOU Y, PIRSKANEN R, LEFVERT AK: Dinucleotide repeat expansion in the CTLA-4 gene leads to T cell hyper-reactivity via the CD28 pathway in myasthenia gravis. *J Neuroimmunol* 2000; 105: 69-77.
90. KOUKI T, SAWAI Y, GARDINE CA, FISFALEN ME, ALEGRE ML, DEGROOT LJ: CTLA-4 gene polymorphism at position 49 in exon 1 reduces the inhibitory function of CTLA-4 and contributes to the pathogenesis of Graves' disease. *J Immunol* 2000; 165: 6606-11.
91. STEINER K, MOOSIG F, CSERNOK E, SELLENG K, GROSS WL, FLEISCHER B, BROKER BM: Increased expression of CTLA-4 (CD-152) by T and B lymphocytes in Wegener's granulomatosis. *Clin Exp Immunol* 2001; 126: 143-50.
92. DAY CJ, HEWINS P, SAVAGE CO: New developments in the pathogenesis of ANCA-associated vasculitis. *Clin Exp Rheumatol* 2003; 21 (Suppl. 32): 35-48.
93. CSERNOK E, ERNST M, SCHMITT W, BAINTON DF, GROSS WL: Activated neutrophils express proteinase 3 on their plasma membrane *in vitro* and *in vivo*. *Clin Exp Immunol* 1994; 95: 244-50
94. BROOKS CJ, KING WJ, RADFORD DJ, ADU D, MCGRATH M, SAVAGE CO: IL-1 beta production by human polymorphonuclear leucocytes stimulated by anti-neutrophil cytoplasmic autoantibodies: relevance to sys-

temic vasculitis. *Clin Exp Immunol* 1996; 106: 273-9.

95. RALSTON DR, MARSH CB, LOWE MP, WEWERS MD: Antineutrophil cytoplasmic antibodies induce monocyte IL-8 release. Role of surface proteinase-3, alpha1-antitrypsin, and Fcgamma receptors. *J Clin Invest* 1997; 100: 1416-24.
96. NORONHA IL, KRUGER C, ANDRASSY K, RITZ E, WALDHERR R: *In situ* production of TNF-alpha, IL-1 beta and IL-2R in ANCA-positive glomerulonephritis. *Kidney Int* 1993; 43: 682-92.
97. ROUX-LOMBARD P, LIN HC, PETER JB, DAYER JM: Elevated serum levels of TNF soluble receptors in patients with positive anti-neutrophil cytoplasmic antibodies. *Br J Rheumatol* 1994; 33: 428-31.
98. MURAKÖZY G, GAEDE KI, RUPRECHT B *et al*.: Gene polymorphisms of immunoregulatory cytokines and angiotensin-converting enzyme in Wegener's granulomatosis. *J Mol Med* 2001; 79: 665-70.
99. TURNER DM, WILLIAMS DM, SANKARAN D, LAZARUS M, SINNOTT PJ, HUTCHINSON IV: An investigation of polymorphism in the interleukin-10 gene promoter. *Eur J Immunogenet* 1997; 24: 1-8.
100. 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: 933-42.
101. LAMPRECHT P, BRUHL H, ERDMANN A *et al*.: Differences in CCR5 expression on peripheral blood CD4+CD28- T-cells and in granulomatous lesions between localized and generalized Wegener's granulomatosis. *Clin Immunol* 2003; 108: 1-7.
102. KOTTILIL S, SHIN K, PLANTA M *et al*.: Expression of chemokine and inhibitory receptors on natural killer cells: effect of immune activation and HIV viremia. *J Infect Dis* 2004; 189: 1193-8. Epub 2004 Mar 16.
103. ZHOU Y, HUANG D, FARVER C, HOFFMAN GS: Relative importance of CCR5 and antineutrophil cytoplasmic antibodies in patients with Wegener's granulomatosis. *J Rheumatol* 2003; 30: 1541-7.
104. GOMEZ-REINO JJ, PABLOS JL, CARREIRAPE *et al*.: Association of rheumatoid arthritis with a functional chemokine receptor, CCR5. *Arthritis Rheum* 1999; 42: 989-92.
105. HEWINS P, SAVAGE CO: ANCA and neutrophil binding. *Kidney Blood Press Res* 2003, 26: 221-25.
106. DIJSTELBLOEM HM, SCHEEPERS RH, OOST WW *et al*.: Fcgamma receptor polymorphisms in Wegener's granulomatosis: risk factors for disease relapse. *Arthritis Rheum* 1999; 42: 1823-7.
107. 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: 574-7.
108. 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: 198-205.
109. MATHIESON PW, PETERS DK: Deficiency and depletion of complement in the pathogenesis of nephritis and vasculitis. *Kidney Int Suppl* 1993; 42: 13-8.
110. 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: 379-82.