pathogenesis [13]. The relative contributions to pathogenesis of PR3 as an auto-antigen and as an enzyme are of interest and warrant further examination. The finding of association at the MHC with MPO-ANCA disease suggests that this too might be driven by anti-MPO auto-reactivity.

Despite their genetic differences, PR3-ANCA and MPO-ANCA disease have similar clinical phenotypes. This may arise because once tolerance to distinct neutrophil proteins has been broken, the resultant ANCA drive disease through similar mechanisms that are essentially independent of antigen specificity. Shared environmental, or common genetic factors not detected by this study, may also strengthen disease similarities. Despite these similarities, the fact that PR3- and MPO-ANCA disease have different genetic etiologies suggests that clinical trials which have considered AAV as one entity may need to be reinterpreted as the two conditions may respond differently to therapeutic intervention.

This first GWAS in AAV has confirmed a genetic component to AAV pathogenesis and demonstrated that GPA and MPA are distinct genetic entities. The genetic associations seen at the MHC, SERPINA1 and PRTN3 loci are better explained by ANCA specificity than clinical diagnosis. Future genetic and clinical studies will clearly need to be powered to detect associations with these conditions separately.

Disclosure of interest: the authors declare that they have no conflicts of interest concerning this article.

References


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1On behalf of the European Vasculitis Genetics Consortium.

Available online 11 March 2013

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http://dx.doi.org/10.1016/j.jlpm.2013.02.303

L32. ANCA vasculitis over the world. What do we learn from country differences?

The epidemiology of the ANCA vasculitides (AAV) [granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA)] has been increasingly well documented over the past two decades in a number of different populations, and it is becoming clear that there are major differences in the occurrence of these three diseases across populations. The aetiology of the AAV is unknown but they are considered to be autoimmune conditions and like most autoimmune conditions represent the interaction between an environmental factor, usually unknown, and a genetically predisposed host. Known environmental triggers (drugs e.g. hydralazine, propylthiouracil) and silica are more frequently associated with MPO-ANCA vasculitis than PR3-ANCA vasculitis. Recent developments in knowledge of the genetic background to the AAV especially GPA and increasing knowledge of the occurrence of AAV in different populations have lead us to consider whether the epidemiology of AAV in different populations can now be explained. The majority of studies come from white Caucasian populations of European descent. The highest figures for the occurrence of GPA come from populations of European descent. In Northern
Europe (Norway, Sweden, Germany and the UK), the incidence of GPA is 10–12/million, and the incidence of MPA 3–10/million. In Southern European populations, MPA appears to be slightly more common than GPA [1].

The incidence of GPA has been reported in several other white Caucasian populations (USA, Australia and New Zealand) where it is very similar to Europe. In striking contrast in Japan, GPA is much less common than MPA but the overall incidence of AAV is very similar to Europe [2]. In all the populations studied where comparative data are available, EGPA is less common than GPA or MPA with an annual incidence in the range 0.5–2.0/million and a prevalence of 10–45/million. Ethnicity may also be important. In Paris, a study from a multiethnic urban area reported that the prevalence of AAV in individuals of European descent (104.7/million) was twice that of non-Europeans (52.5/million) [3]. GPA was relatively less frequent than MPA in non-Europeans, and none of the GPA patients came from Africa. The non-European population was derived from the Maghreb, sub-Saharan Africa, Asia, and the Caribbean, and comprised 28% of the study population (1.09/million). In New Zealand, GPA is twice as common in Europeans than Maoris or Asians [4]. Two countries with an apparently higher incidence of MPA than in Europe are Japan and Kuwait. In the Kuwaiti national population, the incidence of MPA is 24.4/million [5]. In Japan, the incidence of MPA is 18.2/million [2], compared to GPA at only 2.1/million. The Kuwaiti study did not provide any data on the occurrence of GPA. Large case series from China suggest that GPA is relatively uncommon compared with MPA but there is no hard epidemiological data from China on incidence or prevalence [6]. In a multi ethnic series from Chapel Hill in the USA, GPA was relatively uncommon in African Americans compared to Whites [7]. Data from elsewhere in the world is lacking, anecdotal evidence suggests that GPA is more common than MPA in Jordan and Syria. In India, GPA and MPA are recognized but there is no epidemiological data [8,9]. In areas where TB and other infections are common, patients presenting with pulmonary granulomata are liable to be misdiagnosed with tuberculosis and ANCA serology is more difficult to interpret [10]. In recent studies of renal biopsies from India, Korea and Japan, GPA is a very uncommon diagnosis (0.7%) but details of the type of vasculitis is generally lacking [11], by comparison European studies report a much higher occurrence of vasculitis in renal biopsies. Case ascertainment, histological reporting and biopsy practice might explain these differences. In Africa, vasculitis is very rarely reported although GPA has been described in Senegal [12].

There is also evidence that the classical association of PR3 with GPA is less strong in non-White populations. In both Japan and China, a larger proportion of patients classified as GPA using conventional classification schemes are MPO-ANCA positive, and the occurrence of PR3-ANCA is relatively uncommon [2,6].

The genetic associations of GPA and MPA are being established, and for GPA begin to provide a possible explanation for the observed distribution of disease. GPA has been associated in several studies with the HLA-DPB1*0401 allele (OR 3.91 and 3.01) [13], PTPN22 620W allele (OR 2.01) [14], and the PI*Z alleles of the alpha-1 antitrypsin gene [15]. The HLA-DPB1*0401 allele appears to be only associated with GPA and not MPA or EGPA [16]. In Han Chinese, PR3-ANCA vasculitis has been associated with HLA-DRB1*1202 [17]. HLA-DRB1*1501 has been associated with PR3-ANCA vasculitis in both African Americans (OR 73.3) and Caucasians (OR 2.2) [7]. The Genome-Wide Association Study has provided further evidence about the genetic background of AAV [18]. The patients studied were from the UK and Northern Europe where the classical links between disease (GPA or MPA) and ANCA specificity are closest. PR3-ANCA disease was associated with HLA-DR, SERPINA1 and PRTN3, while MPO-ANCA disease was associated with HLA-DQ, SERPINA1 encodes alpha-1 antitrypsin, a serine protease, which has PR3 as one of its substrates. PRTN3 encodes proteinase 3 (rs62132295). Thus the immune response against the autoantigen PR3 is a central aetiological feature of PR3-ANCA associated vasculitis. Haplotype analysis suggested that the causal variant at SERPINA1/SERPINA11 is either the z allele of SERPINA1 or in close linkage disequilibrium with it. The precise variant in the HLA-DP was not determined but there was evidence of only a single genetic association in this region. The strongest SNP associations were with ANCA specificity and not with the clinical syndromes. The study did not confirm previously reported polymorphisms in CTL4A and PTPN22 genes. The actual causal variants, however, remain to be completely elucidated. The global distribution of Pi*Z alleles of SERPINA1 has been well studied because of the association of alpha-1 antitrypsin deficiency with pulmonary and hepatic disease. De Serres and colleagues collated all the available data on the global prevalence of the Pi*Z allele and showed that there are striking geographical differences in prevalence [19]. The Pi*Z allele is most frequently found in Scandinavia (7–27/1000), Western and central Europe (7–30/1000) and those countries colonized by Europeans (North America, 10–12/1000), Australia and New Zealand (12–26/1000). The Pi*Z alleles are rare in China, Japan, Indonesia (0–1/1000). The Pi*Z allele is believed to have arisen in Scandinavia 66–216 generations ago [20]. The HLA-DPB1*0401 allele also shows a variation worldwide [21]. In Europe, there is a fairly consistent allele frequency of around 0.36–0.47. The allele is much less frequent in Japan (0.050), China (0.095 – Han Cantonese) and US African Americans (0.104); three populations where PR3-ANCA vasculitis is very much less common than in Europe. In a small population of Han Chinese, PR3-ANCA vasculitis was associated with DRB1*1202 which is relatively more common in that population than in Europe [17]. In the USA, DRB1*15 was associated with PR3-ANCA vasculitis in both Caucasians and African Americans.
[7]. There was a difference in the genotype associations, DRB1\(^*\)1501 was associated with disease in African Americans whereas DRB1\(^*\)1503 was underrepresented. The DRB1\(^*\)1501 allelic variant is of Caucasian descent whereas DRB1\(^*\)1503 is of African American descent. All the Caucasian patients in this study were DRB1\(^*\)1501. There is little available data on the global distribution of the rs62132295 SNP of PRTN3.

It is therefore possible to hypothesize that the relatively infrequent occurrence of PR3-ANCA vasculitis in China and Japan is a result of the low frequency of two of the three genetic variants (HLA-DPB1\(^*\)0401 and the PI*Z allele of Serpina1) responsible for development of PR3-ANCA vasculitis following an appropriate trigger. We would predict therefore that PR3-ANCA vasculitis would be uncommon in other populations with low frequencies of both these markers in particular other far eastern countries such as Indonesia, and the Philippines. In the absence of data on the distribution of PRTN3 alleles, it is impossible to develop a model to more accurately predict the occurrence of PR3 vasculitis in various communities analogous that recently reported for IgA nephropathy [22].

In conclusion, there are pronounced geographic and ethnic variations in the occurrence of the AAV, especially GPA and MPA. GPA appears to be more common in populations where both HLA-DPB1\(^*\)0401 and the PI*Z allele of Serpina1 are relatively common. More data on the occurrence of GPA in different populations and the distribution of the PRTN3 allele are required to develop a more sophisticated model to explain the occurrence GPA. For MPA, the genetic data is currently less clear. The HLA association appears to be different DQ vs DP but the exact association is unknown. MPO vasculitis can be triggered by drugs and environmental agents so the balance between environment and genetic/ethnic factors may differ between the two main AAV.

Disclosure of interest: the authors declare that they have no conflicts of interest concerning this article.

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Available online 6 March 2013

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http://dx.doi.org/10.1016/j.jrpm.2013.01.032

16th International Vasculitis & ANCA Workshop

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