Disease extent is better evaluated in early large-vessel vasculitis by techniques able to reveal early vascular changes, i.e., vessel wall thickening and mural inflammation (CDS, MR and CT). CDS lends itself particularly well to examining superficial vessels (epiaortic vessels, renal arteries and limb arteries), while CT and MR can also depict deep vessels such as the aorta. Alternatively, PET can be used. PET can reveal active inflammation in most vessels potentially affected by GCA and TAK except the temporal and renal arteries and is probably more sensitive than MR. Monitoring of luminal changes over time requires morphological imaging including CDS, MRA, CTA or DSA.

In GCA, disease severity is mainly related to morbidity, while mortality is very rarely increased (in patients with thoracic aorta involvement that incur dissection). Risk factors for GCA-related ischemic events including visual loss comprise previous ischemic events, marked intimal hyperplasia on temporal artery biopsy, moderately (but not very high) serum inflammatory markers, older age at diagnosis, hypertension, previous ischemic heart disease and absence of systemic manifestations.

**Medium-vessel vasculitis**

PAN is the paradigm medium-vessel vasculitis. Disease extent is typically determined by clinical manifestations, if required supported by DSA especially to detect visceral vessel (micro-)aneurysms. The BVAS can also be used to systematically define the organs involved. Age over 65 years, hypertension, and severe gastrointestinal manifestations are independent predictors of death, whereas patients with cutaneous manifestations or PAN unrelated to chronic hepatitis B virus have a higher risk of relapses. An important prognostic tool for PAN is the five-factors score (FFS), which has been validated in a cohort of patients with PAN (which also included patients with microscopic polyangiitis [MPA]) and Churg-Strauss syndrome (CSS). The FFS includes five items:

- proteinuria greater than 1 g/24 h;
- serum creatinine greater than 140 µmol/l (1.58 mg/dl);
- specific cardiomyopathy;
- specific digestive system involvement;
- specific central nervous system involvement.

Five-year mortality rate is 12% when the FFS = 0, 25% when the FFS = 1, and 50% when the FFS ≥ 2. However, the FFS does not predict the risk of relapses. A revised version of the FFS (FFS2) has been validated for use in PAN, MPA, CSS and granulomatosis with polyangiitis (GPA). The revised FFS2 comprises five items, four with a positive score (+1) and one with a negative score (−1). The four items scoring positive are age over 65 years, cardiac involvement, gastrointestinal involvement and renal failure (creatinine > 1.7 mg/dl), while the item conferring a negative score is ENT involvement. Five-year mortality rate is 7.5% when the FFS2 = 0, 20% when the FFS2 = 1, and 47% when the FFS2 superior or equal to 2.

**Small-vessel vasculitis**

AAV affect small and small-medium vessels and comprise GPA, MPA and CSS. According to OMERACT 2011, the BVAS should be used to measure disease extent and activity in patients with AAV. The BVAS has also a prognostic value, with very high scores predicting fatal outcomes. A BVAS specifically generated for patients with GPA (BVAS/WG) is available. According to BVAS/WG, severe (life or organ threatening manifestations) include skin gangrene, scleritis, retinal involvement, sensineurial hearing loss, mesenteric ischemia, alveolar hemorrhage, respiratory failure, an active urinary sediment with red cell casts, progressive renal failure and neurological involvement. Furthermore, as mentioned above, the FFS (2) can also be used to predict outcomes and thus tailor treatment accordingly. Finally, to assess the extent of both disease- and drug-induced damage OMERACT recommends that the Vasculitis damage index (VDI) be used.

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**L31. A GWAS in ANCA-associated vasculitis: Will genetics help re-define clinical classification?**

Autoimmune diseases are a significant public health problem and are increasing in prevalence worldwide. They are a major cause of chronic morbidity as well as premature mortality. Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) is a severe, systemic autoimmune disease characterised by vascular inflammation and the presence of circulating auto-antibodies against neutrophil granule components, primarily proteinase 3 (PR3) and myeloperoxidase (MPO). AAV, which has a prevalence of 145/million in the UK [1], is comprised of
Three clinical syndromes — granulomatosis with polyangiitis (GPA, formerly known as Wegener’s), microscopic polyangiitis (MPA) and the uncommon Churg–Strauss syndrome (which will not be discussed further) [2]. GPA is most commonly associated with the presence of ANCA targeting PR3 (PR3-ANCA, 66% of cases), while MPA is more commonly associated with ANCA targeting MPO (MPO-ANCA, 58% of cases) [3]. In addition to being a useful diagnostic tool, animal studies suggest that ANCA may be an important driver of disease pathogenesis.

Although patients with GPA and MPA have historically been considered as a single entity when it comes to treatment strategies and enrolment into clinical and genetic studies; there is a growing debate as to whether they are in fact part of a single disease spectrum or represent distinct clinical entities [4]. Clarification of this point would provide a rationale for considering separate treatment strategies for the two syndromes.

While the etiology of AAV is unclear, recent studies have clearly demonstrated a genetic component. The most convincing genetic association is with the histocompatibility complex (MHC) region on 6p21 [5]. While other genetic associations have been reported none have reached the threshold required for claiming genome-wide significance, and thus, while interesting, require further confirmation [6–8]. We performed a genome-wide association study (GWAS) in AAV in order to identify further genetic risk factors and to evaluate whether GPA and MPA have a common or distinct genetic background [9].

The GWAS was performed on 2687 AAV patients of European ancestry and 7650 matched controls. A discovery cohort of 1233 UK cases was genotyped using the Affymetrix SNP6 platform and compared to 5884 Wellcome Trust Case Control Consortium controls. This analysis was consistent with both MHC and non-MHC loci showing associations with disease. Based on this analysis, 158 single nucleotide polymorphisms (SNPs) were taken forward for replication and genotyped using the Sequenom MassARRAY platform across 1454 Northern European cases and 1666 matched controls. Combined analysis of the two cohorts identified three loci showing association with AAV at a genome-wide significance level, namely the HLA DPB1 locus, the SERPINA1 locus, which encodes alpha-1 antitrypsin, and the PRTN3 locus, which encodes the auto-antigen PR3. A number of other loci fell just short of this threshold and they will require larger studies or meta-analyses to confirm their association with AAV. These observations extend the earlier genetic studies and demonstrate for the first time a convincing association of non-MHC loci with AAV.

To determine whether GPA and MPA are distinct entities or ends of a clinical spectrum we stratified our cohort by clinical diagnosis and reanalysed the most associated SNPs from our initial analysis in this stratified dataset. The HLA DPB1 association differed between GPA and MPA, with the association being restricted to the GPA subset of patients. Although less clear-cut, a similar pattern was seen at both the SERPINA1 and PRTN3 loci, with the association being seen only in the comparison between GPA and controls. These data provide clear evidence that GPA and MPA have distinct genetic associations. A similar subset analysis was performed following stratification of the patient cohort by PR3- and MPO-ANCA specificity. At all three loci associated with AAV there was a clear distinction between the PR3-ANCA and MPO-ANCA subsets. In each case the genetic association was only seen with the PR3-ANCA subset of patients. This was particularly striking for the association at PRTN3, which was much more exclusively associated with PR3-ANCA than with either AAV or GPA. In light of these findings, we performed a genome-wide analysis of the stratified dataset. While this threw up no new associations with the PR3-ANCA subset, it did identify a SNP at the HLA DQ locus that was associated with MPO-ANCA. This association was confirmed by genotyping of the replication cohort, with the SNP reaching genome-wide significance in the analysis of the combined datasets.

To further test the observation that the primary association of these variants was with ANCA specificity rather than clinical diagnosis, we examined the SNP associations in the GPA and MPA patient subsets following stratification for ANCA specificity. Although these analyses were poorly powered due to the small sample sizes, the association signal at HLA DPB1 was only seen in those GPA and MPA patients who were PR3-ANCA positive. Similarly, the association with HLA DQ was only seen in GPA and MPA patients who were MPO-ANCA positive. The precise causal variants at each of the identified loci remain to be determined and will require more detailed fine mapping and functional studies. In light of earlier studies in which weak associations between the rare Z and S (null) alleles at SERPINA1 and AAV have been reported [8,10], we performed some additional genotyping at this locus. Haplotype analysis of this data combined with the data from the tagSNP identified in the GWAS, rs7151526, suggests that the causal variant at the SERPINA1 locus is either the Z allele variant itself or something in strong linkage disequilibrium with it. Fine mapping of the MHC associations with both PR3-ANCA and MPO-ANCA disease will be greatly facilitated by use of the immunochip, which contains dense SNP coverage of the MHC region. The observed genetic differences between PR3-ANCA and MPO-ANCA disease may well have immunopathogenic and therapeutic implications. As has been seen previously in type 1 diabetes [11] and membranous nephropathy [12], the identification of genetic variation in the auto-antigen itself, together with HLA, implies a driving role for antigen-specific autoimmunity in PR3-ANCA disease. It is also conceivable that the enzymatic activity of PR3, possibly modified by autoantibody binding and by alpha-1 antitrypsin, might play a role in disease...
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 autoreactivity. 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 PRRT3 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.

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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 GPA comes from populations of European descent. In Northern Europe