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AUTOIMMUNITY

AAV encompasses two major genetically distinct conditions with different autoantibody specificities

The two major clinical syndromes of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)—granulomatosis with polyangiitis (GPA, formally Wegener's granulomatosis) and microscopic polyangiitis (MPA)—are genetically distinct, according to new genome-wide association study data.

Combined analysis of a UK discovery cohort and a Northern European replication cohort (2,687 patients with AAV and 7,650 controls in total), showed significant genome-wide associations between AAV and four single nucleotide polymorphisms (SNPs): three located in the MHC region and one in the *SERPINA1* gene, which encodes the proteinase 3 inhibitor, α-1 antitrypsin. The SNP in the MHC region that showed the strongest association with AAV was located in the *HLA-DP* gene ($P = 4.1 \times 10^{-36}$).

Further subgroup analyses showed differences in the genetic associations of GPA and MPA. However, the strongest associations were with the autoantigen specificity of ANCA rather than with the clinical syndrome.

The four SNPs that were identified in the combined analysis associated with GPA and proteinase 3-ANCA, but did not associate with MPA or myeloperoxidase-ANCA. The associations of these SNPs with proteinase 3-ANCA were stronger than the associations with GPA. A SNP in the *PRTN3* gene, which encodes proteinase 3, was also more strongly associated with GPA than MPA, although this association was not significant. However, the *PRTN3* SNP was significantly associated with proteinase 3-ANCA.

These data suggest a central role of proteinase 3 in the pathogenesis of antiproteinase 3-AAV. A SNP in the *HLA-DQ* gene that significantly associated with myeloperoxidase-ANCA but did not associate with proteinase 3-ANCA, GPA or MPA was also identified.

"AAV encompasses two genetically distinct conditions, one strongly associated with immune reactivity to the autoantigen proteinase 3 and loosely associated with GPA, and the other strongly associated with ANCA specificity for myeloperoxidase and loosely associated with MPA," concludes investigator Kenneth Smith. He suggests that future studies of AAV should be sufficiently powered to allow the identification of autoantibody-specific therapeutic effects.

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