A GWAS In ANCA-Associated Vasculitis: Will Genetics Help Re-Define Clinical Classification?

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Abstract

Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) is a severe condition encompassing two major syndromes – granulomatosis with polyangiitis (formerly known as Wegener’s--GPA) and microscopic polyangiitis (MPA). Its etiology is unknown, and whether it is a single disease entity, and the role of ANCA in its pathogenesis, are debated. To investigate the genetic basis of AAV a genome-wide association study was performed in a discovery cohort of 1,233 UK AAV patients and 5,884 controls, and replicated in 1,454 Northern European cases and 1,666 controls. Major histocompatibility complex (MHC) and non-MHC associations with AAV were demonstrated, and GPA and MPA were genetically distinct. The strongest genetic associations were with the antigenic specificity of ANCA rather than with the clinical syndrome. Anti-proteinase 3 (PR3) ANCA was associated with HLA-DP, SERPINA1 and PRTN3 (p = 6.2 x 10^{-89}, 5.6 x 10^{-12} and 2.6 x 10^{-07}, respectively). Anti-myeloperoxidase ANCA was associated with HLA-DQ (p = 2.1 x 10^{-08}). This study confirms a genetic component to AAV pathogenesis, demonstrates genetic distinctions between GPA and MPA that are associated with ANCA specificity, and suggests that the response against the autoantigen PR3 (encoded by PRTN3) is a central pathogenic feature of PR3-ANCA associated vasculitis.
