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Investigation into the genetic architecture of Giant Cell Arteritis through a genome-wide association study.

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Abstract

Purpose : Giant Cell Arteritis (GCA) is the most common systemic inflammatory vasculitis in people aged over 50 years. It predominantly affects people of Northern European descent and women more than men. It is an ophthalmic emergency and timely diagnosis may prevent significant visual morbidity. The gold standard to diagnose GCA is with a temporal artery biopsy (TAB). To date little is known about the patho-aetiology of GCA. Although there is clear evidence for a role of genetic factors in GCA, genetic studies have been limited in view of the demographic involved, its relatively low incidence rate and the resulting challenge of recruiting an adequately large number of patients. The aim of this work is to investigate the genetic architecture of GCA through a genome wide association study (GWAS) in a large cohort of well-characterised patients with GCA.

Methods : To demonstrate the validity of performing a large multi-centre international GWAS, we performed a pilot study, genotyping a smaller Australian cohort of GCA patients. These patients were recruited through the Arthritis Genomics Recruitment Initiative In Australasia (AGRIA). GCA was confirmed by histopathological examination of TABs with characteristic intimal infiltration with inflammatory cells and fragmentation of the internal elastic lamina. DNA was extracted from peripheral blood and genotyping was performed utilising Illumina OmniExpress SNP array. Quality control measures were applied (excluding SNPs with a call rate <0.97 ; a minor allele frequency (MAF) <0.05 ; or a Hardy-Weinberg equilibrium (HWE) $< 5 \times 10^{-5}$; and samples if they were found to be ethnic outliers or closely related).

Results : Data from a total of 162 GCA patients and a general Australian population set as controls (n=702) were analysed. Following QC a peak of association at the major histocompatibility complex (MHC) was identified. The most strongly associated SNP, rs1264326, achieving genome-wide significance ($P=1.6 \times 10^{-8}$). This SNP is located in the MHC Class I region. No other locus reached genome-wide significance, however four regions reached a suggestive level of significance.

Conclusions : Overall we provide firm evidence for genetic association with GCA. It is likely that with increasing sample sizes additional risk loci will be uncovered. Ongoing work using a large multi-centre international GCA cohort from Australasia and Europe is being undertaken.

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