Estimating the prevalence of misdiagnosis of giant cell arteritis: using a genetic test as umpire

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Background

The diagnosis of giant cell arteritis (GCA) can be confirmed by temporal artery biopsy (TAB). However, TAB is insensitive; therefore, GCA is often diagnosed on clinical grounds despite negative TAB. The prevalence of misdiagnosis in this patient group is unknown. GCA has a strong HLA genetic association [1] that might be used as an umpire test.

Aims

To estimate the prevalence of misdiagnosis of GCA among patients diagnosed with GCA without a positive TAB.

Methods

Cases came from UK GCA Consortium, which recruited patients with a firm clinical diagnosis of GCA. Population control data came from the Wellcome Trust Case Control Consortium. Cases were genotyped using an Illumina genotyping chip [1]. Case and control genomes were jointly imputed using SNP2HLA. A genetic association analysis was carried out, adjusting for the first ten principal components. Misdiagnosis rate was estimated using observed frequencies of nominally-associated variants in the HLA region ($P<0.1$), assuming the GCA patient group was composed of a mixture of genuine GCA cases and misdiagnosed cases.

Results

663 patients diagnosed with GCA (356 with a positive TAB, 147 with a negative TAB and 160 with no TAB result) were compared with 2619 controls. Allele frequencies of 470 variants in the HLA region were compared. The estimated proportion of patients misdiagnosed as GCA was 67% in the negative-TAB group and 33% in the group without TAB result.

Conclusions

The proportion of patients misdiagnosed with GCA can be estimated under certain assumptions. We assumed accurate reporting of TAB and that the cases with genuine GCA with and without a positive TAB are genetically similar. This method could be extended to similar diseases with an insensitive but highly specific reference-standard test and strong genetic susceptibility associations.

Keywords
Imperfect reference standard, umpire test, misdiagnosis, genetic association

References

[1] Carmona et al., *Am J Hum Genet* 100 **2017**, 64-74.