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No evidence for association of a European-specific chromosome 17 inversion with multiple sclerosis

European Journal of Human Genetics (2006) **14,** 1064. doi:10.1038/sj.ejhg.5201665; published online 31 May 2006

Stefansson *et al*[1] recently reported a large inversion polymorphism on chromosome 17q21 that defines two chromosome lineages (H1 and H2) differing in the orientation of a 900-kb segment. Their data indicate that these lineages diverged more than 3 million years ago and have not since recombined. The H2 lineage is rare in Africans, East Asians and indigenous American populations but occurs at a frequency of about 20% in Caucasian populations, where it seems to be undergoing positive selection.

This geographical pattern is congruent with the epidemiology of multiple sclerosis (MS), which is characterised by a high prevalence in European populations and those of European descent, and lower risks for other ethnic groups.[2] Moreover, the inversion lies in a region of suggestive linkage with susceptibility to MS.[3] The 900-kb inverted fragment contains a number of genes including corticotrophin releasing hormone receptor (*CRHR1*), microtubule-associated protein tau (*MAPT*), *N*-ethylmaleimide sensitive factor (*NSF*), saitohin, *LOC284058* and intramembrane protease-5 (*IMP5*).

In order to examine a possible role of the chromosome 17 inversion polymorphism in genetic susceptibility to MS, we typed 937 UK trio families (an affected individual and both parents) for single nucleotide polymorphism (SNP) rs9468 using a TaqMan Genotyping Assay-on-Demand (C_7563752_10, Applied Biosystems). SNP rs9468 is in complete linkage disequilibrium with the inversion, with the C allele perfectly predicting the H2 lineage.[1] Only 76 of the 937 families (8%) included in this study were also part of the previously published linkage screen.[3] There was no significant deviation from Hardy–Weinberg equilibrium and genotyping call rate was 98.5%. No Mendelian errors were observed, nor were any inconsistencies among 166 samples typed in duplicate, indicating a genotyping error rate of $<0.01\%$. In our study population, the H2 lineage had a frequency of 23.7% in 3698 independent parental chromosomes. We did not observe any transmission distortion ($P=0.617$) to affected offspring using the TRANSMIT program.[4]

In conclusion, we have not found evidence that the inversion polymorphism on chromosome 17, which is undergoing positive selection in Europeans, influences susceptibility to MS. This suggests that the modest evidence for linkage with MS seen on 17q results from the effects of other loci in this region.

Acknowledgements
This work was supported by the Wellcome Trust (grant 057097), the Multiple Sclerosis Society of the United States (grant RG3500-A-1) and the Multiple Sclerosis Society of Great Britain and Ireland (grant 730/02). AG is a Postdoctoral Fellow of the Research Foundation – Flanders (FWO – Vlaanderen).

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