Reviewer's report

Title: An investigation of polymorphisms in the 17q11.2-12 CC chemokine gene cluster for association with multiple sclerosis in Australians

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Reviewer: Bernadette Kalman

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Bugeja and colleagues performed a two-stage analysis in the 17q11.2-12 region. After sequencing several DNA pools of MS patients and controls, 48 known and 2 new SNPs were identified within the CCL genes, and served to define minor allele frequencies of markers. Twelve candidate SNPs were selected from this list based on functional considerations for further studies. Seven of these SNPs were genotyped by using the SNaPshot method in 204 MS trios, while 5 of them were genotyped by SNPlex in 373 MS trios. The investigators assessed the distribution of LD, defined the most common haplotypes and determined the minor allele frequencies using the 12 markers. Four individual SNPs showed borderline significance (0.05>p>0.02) in TDT, and without correction for multiple comparisons. A two-marker haplotype within CCL2 and CCL11 also showed transmission distortion, but with a p=0.04 and p=0.05 in the original and in an independent set of trio families, respectively.

Comments:
This is a well illustrated and clearly written study of the 17q11.2-12 region in Australian cohorts of MS families, which presents findings similar to those in two previously published studies of North-American Caucasian cohorts (Ref 42 and 65). Reinvestigation of this well justified candidate region in another (predominantly Caucasian) cohort is very important. However, the interpretation of data appears to be somewhat overstated considering the very weak outcome. Although the outcome was also modest in the North-American cohorts, a marker between CCL2 and CCL7 approached the required p-value after correction for multiple comparisons using 232 SNPs, and transmission distortions of some haplotypes remained significant even after correction for 693 independent tests (reference 65). Nevertheless, as stated in the manuscript, the similar trend of findings is reassuring in the Australian and North-American studies. Another potential criticism concerns the use of relatively few markers (even considering the extensive LD), because of the structural complexity of this chromosome.

Suggestions:
1) Discretionary revision: Add a table to summarize the cohorts studied.
2) Minor revision: Tune down interpretation of data; the paper will still remain an important observation and represent difficulties in complex trait disorders.

What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:
I declare that I have no competing interests