Reviewer's report

Title: Gene expression profiles and genotyping implicate TGF beta-1 and ALOX5 in multiple sclerosis pathogenesis.

Version: 1 Date: 29 August 2007

Reviewer: Pentti Tienari

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General
The authors have analysed gene expression profiles of multiple sclerosis (MS) patients in relapse (n=10) and in remission (n=10). During relapse they found 989 upregulated (p<0.05) genes and 536 downregulated (p<0.05) genes. During remission the respective numbers were 655 and 662, representing slightly different pathways. They then focused on TGFB1 and ALOX5 gene, which were also analysed by RT-PCR. TGFB1 and ALOX5 promoter were sequenced in a DNA pool and the variations found (1 per gene) were tested for genetic association with MS in trio families. A weak association with TGFB1 was found after HLA-stratification (630 trios, p=0.03), but no association was found with ALOX5 in a smaller set of trios (n=102). They conclude that TGFB1 and ALOX5 pathways deserve further study in MS.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
1. Effect of TGFB1 and ALOX5 genotype on their expression level. This is an obvious analysis and should be presented in the remission and relapse cohorts.
2. Association analysis of TGFB1. Only one promoter SNP was tested. This SNP captures only a limited amount of allelic variation of TGFB1. At least 3 non-redundant SNPs should be tested to capture more variation (e.g. rs4803455, rs8179181 or those in previous studies). Haplotype analysis should be performed in addition to single SNP analyses.
3. Association analysis of ALOX5. Only a subset of families (n=102) were analysed for the gggcgg indel. At least 3 non-redundant markers should be tested in the full set of trios in order to obtain a more powerful analysis of this potentially interesting gene.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
Subjects and methods. Were same patients analysed in remission and relapse, or were they entirely different?
The figure should include TGFB1 expression data of patients in remission.
Discretionary Revisions (which the author can choose to ignore)
The authors first made a global gene expression analysis and then focused on just two genes, TGFB1 and ALOX5. The rationale for selecting these two should be more clearly stated.

**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.