Reviewer's report

Title: Gene expression profiles in Finnish twins with multiple sclerosis

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Reviewer: Bernadette Kalman

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Using the BD AtlasTM Human Microarray system, Srkijrvi et al tested the differential expression of 8300 genes in mononuclear cells of eight MZ twin pairs discordant for MS. Twins were selected from the Finnish Twin Cohort Study. Patients had definite MS based on Posers criteria, and were in remission at the time of sample collection. Co-twins were disease free based on clinical and MRI criteria. Half of the patients received IFNβ-1b while the rest was untreated. Over a two-fold up-regulation of six genes was found in 40% of affected twins as compared to the non-affected pairs. The differential gene expression was confirmed by quantitative RT-PCR for the interferon-alpha-inducible protein (GIP3) normalized to G6PDH. The authors conclude that the six identified genes may be involved in the pathogenesis of MS.

General comments:

The observations are of great interest to the MS community, and the manuscript is clearly written. Comparing the mRNA repertoire of MZ twins discordant for MS is a very attractive approach that has been successfully used before (Ann Neurol 1996;40:108-112). In addition, the present study may be the largest molecular study in MZ twins discordant for MS.

There are, however, some issues which influence the interpretation of data and need clarification.

Minor essential revision:

1. Four of the 8 patients were treated with IFNβ-1b. For how long had been these patients on the medication, and for how long had been the remaining 4 patients free of disease modifying treatments (Table 1)? Did the patients receive any symptomatic medication?
2. Three of the four patients with more than 2-fold increase in the GIP3 were on IFNβ-1b. It should also be noted what proportion of patients with up-regulation of the MX2, another interferon-responsive gene, were treated with IFNβ-1b. If both the GIP3 and MX2 over-expression resulted from a treatment response, we are only left with 4 differentially expressed genes in 40% of patients. Nevertheless, if the differential expression of these genes is confirmed in a larger patient control population (a study is already in progress as indicated in the Conclusion), the finding will have a great potential to improve our understanding of MS.
3. Please, include in the citation the study using the MS twin approach (Ann Neurol 1996;40:108-112).

Discretionary revision:

1. Was Sp3 included in the BD Atlas microarray?
2. Although it is unlikely that 40% of patients would differentially express the same genes due to random events, an estimate of the non-disease related expression variations would be of interest (e.g. the inclusion of a few unaffected MZ twin pairs would have been useful). Figure 1 provides information regarding the expression variation of genes of interest among twin pairs. Maybe a housekeeping gene should be included in this figure as reference information.
3. What is the explanation for the decreased β-actin expression in at least 2 of 8 affected patients compared to their co-twin pairs (Table 3)?
In summary, the investigators used a unique and attractive approach to identify candidate molecules in MS. The study was conducted in a rigorous way and the observations merit further investigations. The description of patients and presentation of data need to be somewhat refined.

**What next?**: Accept after minor essential revisions

**Level of interest**: An article of outstanding merit and interest in its field

**Quality of written English**: Acceptable

**Statistical review**: No

**Declaration of competing interests**: I have no financial or non-financial competing interest.