Reviewer's report

Title: Prediction of acute multiple sclerosis relapses by transcription levels of peripheral blood cells

Version: 1 Date: 6 January 2009

Reviewer: Jun-ichi Satoh

Reviewer's report:

General comments

“Prediction of acute multiple sclerosis relapses by transcription levels of peripheral blood cells” by Gurevich et al.

By analyzing predictive models following the algorithm based on SVM and L20OCV, the present study was designed to determine if the expression of subsets of genes in PBMC, serving as a two-stage predictor composed of FLP and FTP, could predict the time to next acute relapse in patients with MS. By focusing on a gene expression dataset of 62 definite MS and 32 CIS patients, the authors identified the 3 best 10-gene FLPs that predict the next relapse with a resolution of 500 days at an error rate of 0.079 and the 4 best 9-gene FTPs that predict the forthcoming relapse with a resolution of 50 days at an error rate of 0.35, both of which are much lower than the error rate of random predictions. The predictor genes are enriched in the TGFB-related signaling pathway. The power of the predictors is neither affected by treatment with different immunomodulatory medications nor by the severity of relapses and several confounding variables. Finally, they concluded that the identification of predictors from gene expression data of PBMC provides a useful tool to predict the disease activity of MS and other relapsing-remitting autoimmune diseases. Overall, the present study is well designed in view of application of bioinformatics and statistics, although supplemental contents are uploaded too much in a poorly organized fashion, making the interpretation of these contents complicate. Following points should be carefully addressed.

(a) Major Compulsory Revisions

1. Since in the present study, relapse is defined as the onset of objective neurological symptoms/signs, clinically silent but neuroradiologically definite relapses detectable only on MRI are totally neglected. The authors should provide an appropriate explanation to compensate for this.

2. The study population of MS and CIS should exclude the subjects with neuromyelitis optica (NMO) by measuring anti-AQP4 antibody in the serum.

3. In the pathway analysis of FLP and FTP (Figure 5), IL24 upregulates IFNG that downregulates TGFB2. TGFB2 downregulates both CA2 and MEFV. The network suggests a counteracting regulation between IL24 and TGFB2, and
between TGFB2 and CA2 or MEFV. However, the list of FLP1 assumed that all of these genes are regulated positively in the same direction. The authors should explain for this discrepancy.

4. The 4 best 9-gene FTPs predict the next relapse with a resolution of 50 days at an error rate of 0.35. I could not understand well why the authors set the resolution period as 50 days, but not 30 days (one month) or 90 days (three months).

5. If the predictor sets of gene expression data of PBMC could accurately predict distant relapse after a long-term latency, PBMC of MS patients intrinsically contains the preactivated genetic program essential for inducing far future relapses. However, the lists of FLP did not tell us much about the relapse-associated molecular mechanism as described in Discussion (p. 11).

(b) Minor Essential Revisions

1. Figures 1-9 are all mislabeled, e.g. Figure 9 should be relabeled as Figure 6.

2. There exist several grammatical and typographical errors and redundant expressions. Neurological symptomatology should be neurological symptoms. Psoriatic arthritic should be psoriatic arthritis.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.