Reviewer's report

Title: Genome-wide Associations of Signalling Pathways in Glioma Subtypes

Version: 2 Date: 7 November 2012

Reviewer: Sven Nelander

Reviewer's report:

The article by Wuchty et al introduces a new approach to associate copy number altered loci and pathways. It does so by first identifying altered genes by pathway enrichment statistics, followed by application of random forest methodology to associate CNAs to the average expression levels of selected pathway genes. For glioblastoma multiforme, the method uncovers well-established chromosomal alterations, and for oligodendrogliomas, new regions are proposed. The paper is interesting as an example of how to gain biological interpretability from cancer genomics data, is clearly written, is metodologically sound (comment below), and should be of interest to specialized readers in the fields of neurooncology and computational methods. I recommend publication.

My main comment is that it is not sufficiently clear from the text what normal samples are used (normal brain? other tissues? cultured cells?) and how the choice of reference might significantly alter the results. It would be important to clarify this before publication.

It is not clear whether the simulation approach used to obtain p-values controls for multiple testing. Is a separate p-value calculated for each association, or is there some form of global correction, please clarify.

Minor comment: the fact that genes have a high gsea score, here termed 'leading edge genes', does not imply that such genes 'drive the pathway', which is a recurring statement in the results section. More, generally, it is not clear what 'drive a pathway' means, so it would be better to use much more neutral language ('pathway members with a high expression relative to a reference panel of noncancer tissues' or similar).

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

Quality of written English: Acceptable

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