Reviewer's report

Title: ATHENA: A Knowledge-Based Hybrid Backpropagation-Grammatical
Evolution Neural Network Algorithm for Discovering Epistasis among Quantitative
Trait Loci

Version: 1 Date: 5 July 2010

Reviewer: Jason Moore

Reviewer's report:

This is a very well-written paper that addresses the important issue of detecting
gene-gene interactions in genetic association studies. The use of expert
knowledge is particularly encouraging.

Major Compulsory Revisions

1) Heritabililty of quantitative traits is usually defined in terms of variance
components and not \( R^2 \). Heritability in the narrow sense is defined as a function
of the additive genetic variance component. Please reconcile this. Also, as you
using unbiased estimates? See the paper by Boerwinkle and Sing (1986).

Boerwinkle E, Sing CF. Bias of the contribution of single-locus effects to the

2) Can you show what one of your NN models looks like for one of your data
models? This would help the reader conceptualize the approach.

3) Comparing the models you get from the NN with those one could obtain from
CPM/RPM and linear regression would be helpful. Could you add a brief
discussion of this to the end of the paper? You might cite and discuss the
following two papers.

Culverhouse R, Klein T, Shannon W. Detecting epistatic interactions
contributing to quantitative traits. Genet Epidemiol. 2004 Sep;27(2):141-52.

Hamon SC, Stengard JH, Clark AG, Salomaa V, Boerwinkle E, Sing CF.
Evidence
for non-additive influence of single nucleotide polymorphisms within the

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:

I declare that I have no competing interests