Reviewer’s report

Title: Genome Screen in Familial Intracranial Aneurysm

Version: 2 Date: 17 October 2008

Reviewer: Gerard Tromp

Reviewer’s report:

This is a well-executed study that addresses the important medical question of genetic predisposition to intracranial aneurysms. It is one of the larger sample-size linkage studies performed. Overall the manuscript is well written and cites relevant prior publications.

The authors address the advantages and most of and limitations of the study. What is not addressed well is the effect of the screening high-risk individuals. One of the criteria for high-risk is smoking. Since smoking is an important independent risk factor for IA, selecting smokers for screening may, in fact, increase the proportion of cases whose IA is predominantly due to environmental factors, i.e., whose genetic component of the disease is very low. Thus, although from a medical perspective it make sense to screen to screen high-risk individuals, from a genetic perspective it can reduce power. Authors should address that as a potential limitation. Related questions are what fraction of cases were discovered on screening and what fraction of the families had a high proportion of screened cases?

Linkage is a method generally not considered sensitive for detecting alleles with low relative risk or weak effect since alleles with low relative risk, or penetrance, do not result in detectable familial aggregation. Is it therefore surprising that the analysis did not detect linkage to the chromosome 9p21 risk allele? What is lowest relative risk that the study would detect?

The results of the model-based analyses favor the few genes with relatively large effect in some subset of the families.

Major Compulsory Revisions

None

Minor Essential Revisions

Discuss the potential limitation on detecting genetic loci due to screening individuals with a high environmental component to their disease.

Provide indication of what fraction of cases were detected by screening and what fraction of families had high proportion of screened cases.

Discuss the limitation(s) of linkage for detecting alleles with weak effect.

Discretionary Revisions
None

**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