Reviewer's report

**Title:** Gender Bias Association with the Mitochondrial Haplogroup JTU Cluster in Patients with Age-related Macular Degeneration: A Case Control Study

**Version:** 1  **Date:** 27 July 2012

**Reviewer:** Arthur Bergen

Reviewer's report:

The authors present an essentially confirmatory association study that the JTU mitochondrial haplotype is associated with AMD. The study (design) is straightforward, and the results are well presented and presented. The authors claim for the first time a JTU related gender effect, with males having a higher risk compared to females. I have only a few comments (minor essential revisions)

- The number of patients and controls in this association study is limited, but the results essentially confirm previous studies and reinforce those. Since multiple AMD risk factors may be population dependent, the study is of value.

- Introduction: Although there’s no doubt that light exposure to the retina causes oxidative stress, which is indeed involved in AMD, most blue and ultraviolet light is filtered out by the lens and does not reach the retina at all.

- In the introduction section the authors should state that heterogeneity of AMD risk factors across populations is the rule rather than the exception (read for example recent AMD association articles by Baas DC et al), and that this also probably holds for their data to be presented in this manuscript. Indeed, apart from the gender issue, this is essential since it is one of the merits of the study.

- In the results section, the authors state “indicating that having a JTU background did not have additive risk for the ARMS2-rs10490924 or CFH-rs1061170 SNPs when compared to the H haplogroup background”. They should reformulate this more carefully since the power of their study is quite low, and interactions between risk factors and genetic background or vice verca in their study are likely to yield non-associations anyhow.

- Although not essential, the study would gain interest if the authors could perform a meta-analysis incorporating similar “raw” data from previous studies.

- Somewhere in the discussion I miss a statement that, since oxidative stress appears to be involved in both aging and age-related diseases careful assessment of the age of all control populations is essential. Minor aging differences/effects may already yield false positive associations.

Can the gender effects also be explained by differences in the (average) age of males and females in the control population? Is the number of males compared to females different in the diseased and control population, so that the putative...
difference in “strength” of the association merely reflects power of the same effect, and not a genuine difference? If not, what would be an alternative explanation for this presumed effect?

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

'I declare that I have no competing interests’