Reviewer's report

**Title:** Polymorphisms in the glutathione pathway modulate cystic fibrosis severity: a cross-sectional study

**Version:** 5  **Date:** 17 June 2013

**Reviewer:** Harriet Corvol

**Reviewer's report:**

**Major Compulsory Revisions**

As highlighted in this study, it is now recognized that, besides the CFTR genotype, other genetic factors could contribute to the cystic fibrosis (CF) phenotype. The authors studied whether genes associated with the glutathione (GSH) metabolism could influence CF severity. While this study may be of interest, major commentaries could be raised:

- Compared to the current published studies on modifier genes in CF, the cohort is very small: 180 patients and no replication.....it is well known that such a small cohort could provide false-positive results, especially if there is no replication in an independent population. There are actually large CF cohorts that are being internationally collected with a main aim to study such modifiers of the CF disease phenotype. The authors should at least acknowledge such collections and cite proper publications (and…please…do not cite reviews but the original papers)!

- For example, a North-American GWAS in a very large CF population did not show any association with lung disease severity in the regions studied by these authors (Wright and coll. Nat Genet 2012) … underlying again the risk of false-positive associations driven by such a small cohort without replication…

- A lot of different phenotypes have been studied: far too many in this far too small cohort. One might expect such a broad phenotype's study only in a much larger cohort.

- The authors have corrected their results for multiple testing using a Bonferroni correction, but what is the “number of tests” referring for?

- The authors studied CF patients with and without pancreatic insufficiency, but it is well known that severity of the CF patients is highly linked to this clinical feature and, at least, a correction should be made…

- It is unclear how did the authors chose the SNPs within the genes studied?

- What are the equation used to calculate the percent predicted FEV1 and FVC? Why do not use, as frequently used nowadays in CF gene modifiers papers, FEV1 CF-specific percentiles?
Level of interest: An article of insufficient interest to warrant publication in a scientific/medical journal

Quality of written English: Not suitable for publication unless extensively edited

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