Reviewer’s report

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

Version: 7 Date: 29 November 2013

Reviewer: Frauke Stanke

Reviewer’s report:

Review for:
Revised version of MS: 1229360747911350; Manuscript „Polymorphisms in the glutathione pathway modulate cystic fibrosis severity: a cross-sectional study” by Fernando AL Marson, Carmen S Bertuzzo, Antônio F Ribeiro and José D Ribeiro

The reviewer thanks the authors for the considerable effort that they have undertaken to improve their manuscript. However, a few points of criticism remain – this might be due to the fact that neither the reviewer nor the authors are native speakers and hence, information gets lost.

Please clarify the following points, still open after last review:

A. for formal reasons:

Question to the authors, last version of this manuscript:
“For clarification: The reviewer understands that this is a resubmission of the data previously submitted to The Journal in a manuscript entitled “Genetic interaction of GSH metabolic pathway genes in Cystic Fibrosis?” The authors have carefully explained how the previous manuscript differs from the present one. However, was the work formerly entitled “Genetic interaction of GSH metabolic pathway genes in Cystic Fibrosis?” published? Based on the phrase “In the context of previously published article, we .....” it can be inferred that the genotyping data was evaluated twice and two manuscripts were derived? If so, is the work referenced in the present manuscript?

B. for scientific reasons:

On the topic of high prevalence of PS patients: apparently, reviewer and authors agree on the survivor bias in the patient sample – see question and answer to 1C. Please reconsider whether you want to keep this important conclusion hidden within the data (or maybe communicate this fact within the section that described the patient’s history).

C. for scientific reasons:

To detect the survivor bias reliably, the reviewer has proposed before to “rank patients according to date of birth. If PS patients are more frequently among early-born individuals, this indicates a survivor effect in the population. Likewise,
if patients with two unresolved CFTR mutations and/or patients with one resolved CFTR mutation and/or patients with two identified CFTR mutations cluster by birth cohort, this indicates a survivor effect in the population.”

The authors have answered that “to understand the frequency for pancreatic sufficiency, having fixed the age of the patient as parameter was calculated, the age difference between the groups of patients with and without insufficiency (Table 13). In the case of groups with and no identified CFTR mutations, after exclusion of patients with pancreatic sufficiency no difference in age was observed.”

This is misleading – the age of the patient was fixed? Was a patient born in 1970, recruited at age 18 in 1987 compared to a patient born in 1980, recruited at age 18 1989? If so, the parameter to be compared between the groups is the year of birth (1970, 1980, different) and not the age (18y, 18y, identical). In other words, if early-born patients are more likely to be PS than patients from later decades, the survivor effect is underlined. This also indicates that other risk alleles than CFTR PI mutations might be depleted from the population, and that in turn might lead weight to moderate P-values when comparing cases and controls for CF modifying genes.

Minor points:
1. The following names are misspelled in the manuscript: Karl Kunzelmann, Frauke Stanke.
2. Table 14: the designation of the patients subset in column 1 are missing; no mutation identified 44, One CFTR mutation identified 51, Two mutation identified 84, (this set: not accounting for PS status?), One CFTR mutation identified 35, Two mutation identified 43, (this set: PI only?)
3. Table 14: heading says “Age’s distribution and osteoporosis among CFTR mutation groups” and the values range between 7 and 1274. These are not years, but?

**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.