Reviewer's report

Title: Large Genomic Rearrangements in the CFTR Gene Contribute to CBAVD

Version: 1 Date: 21 February 2007

Reviewer: Sabina Gallati

Reviewer's report:

General
The authors report on two well known large genomic rearrangements in the CFTR gene detected in two out of 182 males with isolated congenital bilateral absence of the vas deferens (CBAVD) confirming the frequency of large rearrangements to be within the range observed in the classic CF population and thus pointing to the need to offer screening of gross rearrangements to males with CBAVD and only one or none detectable mutation after PCR-based scanning of the CFTR gene.

New aspects of this paper are the development of a simple and rapid duplex PCR test for the specific detection of the two rearrangements as well as the presentation of a bioinformatic tool for exon phasing and the proposition to rename CFTR exons and mutations according to international recommendations.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

- As both rearrangements have been well described before, figure 1 and 2 have to be omitted (as they add no new information) and replaced by one figure demonstrating the two specific junction fragment amplification tests. The text “detection of two complex CFTR large deletions” and “confirmation of deletion breakpoint junctions” in the result part has to be merged and shortened in favour of highlighting the development of the rapid and specific mutation test.

- The UMD software is a nice and helpful tool, but the prediction of an inframe deletion of exon 2 for the CFTRdele2 mutation and the loss of the three last exons for the second rearrangement is not new and the recommendation to rename CFTR exons and more than 1500 mutations needs much more discussion. Change of the CFTR nomenclature can not result from a single action but from a worldwide decision by consensus based on a debate including scientific, diagnostic and quality aspects and stipulated in guidelines.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

- Background (lines 11-13): The statement “a combination of severe genetic changes in the two CFTR alleles that reduces CFTR function below 5% of physiological levels usually leads to the classical manifestation of CF” needs references.

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptence or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests