Author's response to reviews

Title: An association study on contrasting cystic fibrosis endophenotypes recognizes KRT8 but not KRT18 as a modifier of cystic fibrosis disease severity and CFTR mediated residual chloride secretion

Authors:

Frauke Stanke (mekus.frauke@mh-hannover.de)
Silke Hedtfeld (hedtfeld.silke@mh-hannover.de)
Tim Becker (becker@imbie.meb.uni-bonn.de)
Burkhard Tümmler (tuemmler.burkhard@mh-hannover.de)

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Author's response to reviews: see over
Dear Sir,

please find enclosed the 2nd revised version of MS:9170606874860806 “An association study on contrasting cystic fibrosis endophenotypes recognizes KRT8 but not KRT18 as a modifier of cystic fibrosis disease severity and CFTR mediated residual chloride secretion”. As detailed below in our point-to-point responses to the reviewers` comments, we have checked the manuscript for typographical and grammatical errors. Complying with the editorial request, all changes made in the 2nd revised version of the manuscript are highlighted in green.

We hope that the manuscript is now acceptable for publication in BMC Medical Genetics.

Yours sincerely,

Frauke Stanke
Reviewer 1 - Minor essential revision:
- there are a variety of typos throughout the manuscript that require correction; especially in the newly added text. For example, pages 5 and 16.
We have corrected some typographical or grammatical errors. All text that has been changed for the 2nd revised version is highlighted in green throughout the manuscript.

Rev1 Discretionary revision 1
- it is still unclear why the composite parameter is preferable. Some reporting on heritability would clear this up, especially when contrasting heritability across the various possible individual phenotypes from which the composite was calculated.
In our revised manuscript, we explicitly state that “Intrapair discordance was significantly lower in monozygous twin pairs as long as the composite parameter was considered, while no association of intrapair concordance with twin zygosity was seen when only wfh% or only FEVPerC were examined. Interpreting the higher concordance of monozygous twin pairs as an indication of inherited factors that determine the phenotype, we concluded from this finding that the composite parameter was more sensitive to detect inherited factors than either of the individual clinical parameters wfh% and FEVPerC. Consequently, we relied on the composite parameter to select patient pairs with extreme clinical phenotypes for the association study.” In other words, neither of the individual parameters showed an elevated degree of concordance among monozygous twins which results in a high heritability. In contrast, monozygous twins are significantly more concordant in the composite parameter. Consequently, the heritability of the composite parameter must be higher than those of the two individual parameters. Hence, this is why the composite parameter is preferable. We believe that the question of the reviewer is already sufficiently answered and choose not to extend the manuscript text further.

Rev1 Discretionary revision 2
- Seems all discussion of the endophenotype can now be removed since the authors are no longer referring to THEIR phenotype as an endophenotype.
The endophenotypes are referred to throughout the manuscript. (page 5: “.... CFTR mediated residual chloride secretion in the airways or the intestine ....”; page 6 “...with contrasting clinical and basic defect endophenotypes ....”) In the light of the comment of reviewer 3 who states that “there is a large section now discussing endophenotypes”, we feel that the subject of endophenotypes is now adequately covered in the revised version.