

Author's response to reviews

Title: The association between genetic variants in hMLH1 and hMSH2 and the development of sporadic colorectal cancer in the Danish population

Authors:

Lise Lotte Christensen (liselotte.christensen@ki.au.dk)

Bo E Madsen (eskerod@birc.au.dk)

Friedrik P Wikman (fpw@ki.au.dk)

Carsten Wiuf (wiuf@birc.au.dk)

Karen Koed (kako@jcvu.dk)

Anne Tjoennland (annet@cancer.dk)

Anja Olsen (anja@cancer.dk)

Ann-Christine Syvanen (ann-christine.syvanen@medsci.uu.se)

Claus L Andersen (cla@ki.au.dk)

Torben F Orntoft (orntoft@ki.au.dk)

Version: 4 **Date:** 16 May 2008

Author's response to reviews:

Comment to reviewer

1. It is probably not appropriate to include the CRC familial cohort....

Comments from the authors

We do think that these data are important for the reasons listed below

a. The data on the familial CRC cohort was included since the majority of the mutations were initially identified in this cohort. Some variants were found only in one family whereas others were identified in several families in the cohort (Has been added at page 6 in the section subjects/cohort).

b. We wanted to analyze whether some of the variants caused an elevated risk of CRC in a selected cohort with familiar CRC. We speculate that they could cause an increase in cancer susceptibility maybe in combination with other yet unidentified genetic factors present in these families. One of the variants was indeed present with a higher frequency in the CRC family cohort compared to both controls and the sporadic cohort. The following has been added on page 10, Results, Frequency of the variants in the three cohorts: The analyzed variants were initially identified in the familiar CRC cohort and the cohort was included in the study to elucidate whether a common variant could explain the elevated cancer susceptibility in these families.

2. The role of MLH1, MSH2 and MSH6 was ruled out.

Comments from the authors

The role of mutations in these three genes was not ruled out but the presence of

other clearly pathogenic mutations in the three genes was excluded.

The following has been added at page 6 in the section Subjects/cohort; The presence of other clearly pathogenic mutations in the hMLH1, hMSH2 and hMSH6 has been excluded by sequencing.

3. It is odd that the family history characteristic (Amsterdam II positive or negative).....

Comments from the authors

We do not hold detailed information in each individual family but we know from the clinical geneticists that the individuals in the familial cohort are either from Amsterdam positive families or from families with an accumulation of CRC.

The following has been added at page 6 in the section Subjects/cohort: Detailed information on each individual family in this cohort is not available.

4. Page 11, end of 1st paragraph

Comment from the authors

Has been deleted.

5. Typing errors and English style

Comments from the authors

A thoroughly language revision has not revealed many errors. Should there still be typing errors or English style that should be corrected please indicate the location in the text.

Comments to BMC medical genetics

1. Could you also please provide the name of the ethics committee who approved your study?

Comment from the authors: The name is "Regional Scientific Committee on Human Studies" (in either Arhus or Copenhagen). Has been added in the text page 5/6