Author's response to reviews

Title: Germline deletions in the EPCAM gene as a cause of Lynch syndrome-literature review.

Authors:

  Katarzyna Tutlewska (k.tutlewska@wp.pl)
  Jan Lubinski (lubinski@pum.edu.pl)
  Grzegorz Kurzawski (gkurz@sci.pum.edu.pl)

Version: 2 Date: 6 August 2013

Author's response to reviews: see over
Dear Reviewers

Thank You for your opinion and valuable comments. Please find a list of answers on Reviewers comments.

An answer to the Reviewer #1 (Arvids Irmejs):

1. We decided to add to title a phrase “literature review” according to your suggestion
2. An English has been improved
   a. Instead of “due to data from NCBI..” we added “According to data…” page nr. 3, paragraph nr. 1, line nr. 8
   b. We deleted a phrase “due to” in sentence “due to pedigrees typical for LS..” page nr. 4, paragraph nr. 2, line nr. 4
   c. We deleted phrase “is that” in sentence “What is interesting, high expression of EPCAM…” page nr. 5, paragraph nr. 1, line nr. 13
   d. Instead of expression “deletion of 8 and 9 exons of” we put “deletion both exons (8 and 9)” page nr. 11, paragraph nr. 3, line nr. 7
   e. We changed version “was observed also in other studies” to suggested “was also observed in several other studies” page nr. 12, paragraph nr. 2, line nr. 11
   f. page nr. 12, paragraph nr. 3, line nr. 8, we changed the sentence to be more clear, “EPCAM deletion carriers will probably be more easily recognized than carriers of an MSH6 mutation, whose colorectal cancer risk is lower with a higher age of onset (2)”.
An answer to the Reviewer #2 (Andrzej Pławski):

1. Major Compulsory Revisions
We deleted a phrase “heterozygotic” in sentence “Lynch syndrome associated tumors are usually characterized by heterozygotic DNA mismatch deficiency” (Page1, Line 13)

2. In Minor Essential Revisions we agreed with your suggestions in each point, so we changed our expressions for suggested ones (page 3, 4, 5, 11)
   In the revised version we added:
page 3
   “In other words, a MMR gene defect in one allele gives susceptibility to further mutations which may affect second allele cause lack of mismatch repair function in cell.”
Page 4
Appropriate diagnosis of LS may curried out in two major ways. One of them is to focus on an adequate family history in all patients visiting a physician. The revised Bethesda guidelines are probably the most common used criteria for selecting patients with CRC for further molecular tests (10,11) (Table 1). The other way is systematic testing for all patients with CRC for loss of MMR function by means of high level microsatellite instability in tumor tissue or immunohistochemistry (ImmunoHistoChemistry, IHC). The advantage of the immunohistochemistry, is also allowing prediction of which mismatch repair gene is likely to be affected by a germline mutation (10). In our International Hereditary Cancer Center patients are classified to Lynch syndrome according to characteristic clinical features or criteria and pedigrees typical for Lynch syndrome as well, what is presented by Kladny and Lubinski (12). An example of a pedigree of a family with definitive HNPCC and EPCAM carriers is shown in Fig. 2.
In some individuals with Lynch syndrome the MMR genes mutation search fails. This group is of particular interest to researchers, who trying to find the genetic factors causing the disease. In some LS patients it have been shown that MMR genes methylation cause disease occurrence (13, 14, 15, 16).

We replaced our paragraph according to your suggestion

“Our unpublished data from the studies of 55 patients with LS indicates that deletions of 8 and 9 exons of the EPCAM gene mutation determine 7% of LS cases without MMR mutation”