Reviewer’s report

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

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Reviewer: Andrzej Plawski

Reviewer’s report:

1. Major Compulsory Revisions
Page one
Line 13 “Lynch syndrome associated tumors are usually characterized by heterozygotic DNA mismatch deficiency” please check heterozygotic

2. Minor Essential Revisions
Page 3
In other words, a MMR gene defect in one allele gives susceptibility to the loss of the other allele with normal function, and a secondary mutation in this allele will lead to lack of mismatch repair function.
Did you mean loss off alle (deletion) or loss of functionality. You expect mutation in deleted allele
my suggestion is
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
Line 4
This fragmnet in my opinion is rather chaotic
There are many ways to improve the identification of Lynch syndrome. One of them is to focus on an adequate family history in all patients visiting a physician. In our International Hereditary Cancer Center patients are classified to Lynch syndrome according to characteristic clinical features or criteria and due to pedigrees typical for Lynch syndrome as well, what is presented by Kladny and Lubinski (10). An example of a pedigree of a family with definitive HNPCC and EPCAM carriers is shown in Fig. 2.
Many criteria have been proposed to identify LS: mainly based on age at CRC diagnosis, the presence of multiple tumors and the number of affected family members. The revised Bethesda guidelines are probably the most common used criteria for selecting patients with CRC for further molecular tests (such as for MSI; or ImmunoHistoChemistry, IHC) (11) (Table 1).

However, these criteria have been criticized for being too complex and lacking in specificity and sensitivity and therefore they are poorly implemented in clinical practice.

Alternatively to these clinical guidelines, systematic testing has been recommended for all patients with CRC for loss of MMR function by means of high level microsatellite instability in tumor tissue or immunohistochemistry, allowing prediction of which mismatch repair gene is likely to be affected by a germline mutation (11).

My suggestion is replace with:

Appropriate diagnosis of LS may be carried 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 (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 (11). In our International Hereditary Cancer Center patients are classified to Lynch syndrome according to characteristic clinical features or criteria and due to pedigrees typical for Lynch syndrome as well, what is presented by Kladny and Lubinski (10). An example of a pedigree of a family with definitive HNPCC and EPCAM carriers is shown in Fig. 2.

Line 21

The Sentence
A new phenomenon was recently shown, in which the DNA of MMR genes MSH2 and MLH1 can be methylated in some individuals with Lynch syndrome (13, 14, 15, 16).

In this paragraph you describe new phenomenon and new mechanism
The references for “new and recently” are 6 and 7 years old and the phenomenon of methylation is widely known.

My suggestion is to set something like this

In some individuals with Lynch syndrome, the MMR genes mutation search fails. This group is of particular interest to researchers, who are trying to find the genetic factors causing the disease. In some LS patients, it has been shown that MMR genes methylation cause disease occurrence (13, 14, 15, 16).

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as well, in some MMR germline-mutation-negative LS families (18). A new mechanism of

start new paragraph from

A new mechanism of

Page 11

You describe your research but it is a review article

In our study, we have analyzed 55 patients from the Polish population for germline deletions in EPCAM gene. These patients were registered in the International Hereditary Cancer Center in Poland. The cases were selected from the cohort of 768 patients who were classified to have Lynch syndrome according to pedigrees and who were analyzed for appearance of mutation in MLH1, MSH2, and MSH6 genes. This group of patients was diagnosed to be noncarrier of mutations in MMR genes, but they were predisposing to Lynch syndrome due to pedigrees. Based on the MLPA analysis, we have documented deletions of 8 and 9 exons of the EPCAM gene in 4 families.

consider whether replace it by

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

**Level of interest:** An article of importance in its field

**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 no competing interests