Reviewer's report

Title: Common NOD2/CARD15 variants are not associated with susceptibility or the clinicopathologic characteristics of sporadic colorectal cancer in Hungarian patients

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Reviewer: Pia Alhopuro

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General

Lakatos et al examined the possible association of two NOD2 polymorphisms, G908R and 3020insC, with colorectal cancer (CRC) in the Hungarian population using DHPLC. Authors examined 194 consecutive CRC patients and 200 gender-matched healthy controls and found no significant association with CRC risk. In addition, no association with clinicopathologic characteristics was observed. The manuscript is concise and the genotype frequencies observed are in accordance with previous studies in Hungarian controls (Büning et al 2005, Bene et al 2006, Lakatos et al 2005). Although some previous studies have reported an association of one or several NOD2 polymorphisms with CRC risk, others have found no association. Therefore, although the results are essentially negative, the study by Lakatos is of interest and adds to the conflicting literature.

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

1) The materials and methods section should be described in more detail. The number of controls and the genotype frequencies are identical to a previous report by the same authors. Are these the same controls as in (Lakatos et al 2005)? In case they are, it should be mentioned in materials. How were the healthy controls defined (ethnicity, age, origin, definition for cancer-free)? Using unselected CRC cases for family or clinical history would have been interesting. Why did the authors decide to exclude familial cases?

2) It would be more convincing if all the statistical values were presented in Tables 1 and 2 (p-values and ORs). The authors use term “NS” which I assume means non-significant. This should be explained.

3) In previous studies reporting an association of NOD2 variants with CRC, the ORs have typically been ~2.5 or higher. Was the statistical power sufficient to exclude an association of OR 2.5 or 2.0? The manuscript should include a critical discussion of the study power to detect very low-penetrance effects.

4) It would be of great interest if the authors genotyped the CRC patients for R702W as well. This would allow an analysis of combined frequency of all three NOD2 variants as in Roberts et al 2006. Do the authors have any data on R702W in CRC patients? In fact in introduction the authors write “our aim was to investigate the presence of the three common NOD2 variants in a large cohort of patients with sporadic CRC in Hungary”. However, no results from R702W are shown.

5) There are some inaccuracies in discussion. Second paragraph “no other common NOD2/CARD15 mutations were detected in the study”. This refers to the Polish study, in which no other NOD2 polymorphisms were examined. The word “detected” is misleading. Third paragraph “the risk for sporadic CRC cases with or without family history”; the word “sporadic” is unnecessary. Furthermore, the study by Alhopuro et al reported no association of 3020insC with any clinical or tumor characteristics. Compared to patients <50 years of age (4.4%) those >50 years had no higher frequency of 3020insC (4.3%) unlike in study by Kurzawski et al. Could the authors rewrite this part of the paragraph?

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

6) Introduction, first paragraph: Hungary should be with a capital.

7) Gene names are typically written in italics.

Discretionary Revisions (which the author can choose to ignore)
**What next?**: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**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 that I have no competing interests'