Reviewer’s report

Title: Low-penetrance alleles predisposing to sporadic colorectal cancers: a French case-controlled study

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Reviewer: Sergi Castellvi-Bel

Reviewer’s report:

Colorectal cancer (CRC) is an important public health problem, being the second commonest neoplasm in the world and also the second leading cause of death linked to cancer in Western countries. In Europe, there are more than 200,000 new cases and more than 100,000 deaths related to CRC each year.

As seen also in many other cancers, activation of oncogenes and inactivation of tumor-suppressor genes are key events for CRC development and progression. Germline mutations in the genes responsible for the hereditary CRC forms (APC, mismatch repair genes, MYH, LKB1, SMAD4, BMPR1A, PTEN) have been identified in the past 15 years and correspond to high-penetrance, rare genetic components that only explain a very small fraction of CRC genetic susceptibility. On the other hand, more common, low-penetrance genetic variants in a polygenic and additive/multiplicative manner are postulated to be responsible for the more frequent familial CRC.

The manuscript by Küry et al. presents an interesting paper describing a genetic association study with 1023 sporadic colorectal cancer (CRC) patients and 1121 controls assessing the CRC risk linked to 52 polymorphisms in 35 genes involved in biological processes such as inflammation, xenobiotic detoxification, one-carbon metabolism, insulin signaling or DNA mismatch repair. These 52 polymorphisms were formerly involved in low-penetrance CRC predisposition by independent studies and the authors intended to replicate those previous findings in their population.

Their main proposed objective is very reasonable, their CRC patient and control collection is suitable, and methods used are well described and performed. Data and conclusions of this report are remarkable for the CRC genetics research field. Besides, the authors present their results in the appropriate type of article and it falls within the scope of BMC Cancer.

Besides this general comment, other specific comments regarding the scientific content of the manuscript are the following:

Major Compulsory Revisions:
None.

Minor Essential Revisions:
1) In the background section, I would suggest to be cautious in considering equally results from recent whole-genome genetic association studies (references 8-12) to more modest approaches such as the one described in the present article by the authors. These two approaches differ considerably in terms of genome coverage, replication methodology and significance of results.


3) Besides, I would recommend also including a comment regarding the usefulness of a meta-analysis as a step to confirm or refute any genetic polymorphism-disease association.

Discretionary Revisions:

4) Please refer in the text to Genetic association study instead of only association studies.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.