Reviewer’s report

Title: Characterization of the rs2802292 SNP identifies FOXO3A as a modifier locus predicting cancer risk in patients with PJS and PHTS hamartomatous polyposis syndromes

Version: 6 Date: 14 July 2014

Reviewer: Andrzej Plawski

Reviewer’s report:

1. Is the question posed by the authors well defined?
   Authors did no define the aim of study

2. Are the methods appropriate and well described?
   The preparing PCR product is described well. The sequencing in poor described if compare to description of the PCR product preparation

3. Are the data sound?
   YES

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
   Yes

5. Are the discussion and conclusions well balanced and adequately supported by the data?
   There is not detailed data describing genotypes in male and female in group with cancer and without cancer in table. IT would be useful if they will do it due to their conclusion that subgroup analysis for each HPS syndrome revealed a G-allele-associated beneficial effect 50 on cancer risk occurring mainly in males.

6. Are limitations of the work clearly stated?
   YES

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
   YES

8. Do the title and abstract accurately convey what has been found?
   NO. In Abstract there is not aim of studies
   In My opinion the rs2802292 (TT genotype ) shows association with higher risk of malignancies occurrence, it can’t be e predictive

9. Is the writing acceptable?
   For me, YES. I am not English native speaker
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Authors call the STK11 gene as LKB1. Human serine/threonine protein kinase, was previously named LKB1 but renamed STK11. HGNC Approved Gene Symbol is STK11.

The data about allele frequency in male and female should be added in table 2. It allow to check statistics

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

PJS and PHTS hamartomatous polyposis syndromes are two different diseases. In addition, patients presented malignancies various organs. The authors have combined patients into one group in my opinion it is not the best idea. There is no data about the nature of mutations in the genes predisposing to described diseases. Do they not affect the course of the disease? This aspect should be discussed. I aware of the small number of patients available but the divide them into subgroups (male and female) makes an impression of data juggling.

I do not agree that authors found locus predicting cancer risk in patients with PJS and PHTS hamartomatous polyposis syndromes. It may suggest the possibility of exclude GG curriers from further diagnostics. It have to be clarified.

The FOXO3A rs2802292 G-Allele feature was described in article J Clin Endocrinol Metab. 2011 Jan;96(1):E119-24. doi: 10.1210/jc.2010-0881. Position 15 in your references.

It has a positive effect on various functions of the organism. The frequency of allele G in this work, was 45.3%: which is consistent with the MAF previously described for the general population. Is it possible that this is a general effect of allele G, not just for patient with LKB1 and PTEN mutations.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

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.