Reviewer’s report

Title: XPD Codon 312 and 751 Polymorphisms, and AFB1 Exposure, and Hepatocellular Carcinoma Risk

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Reviewer: Jia-Sheng Wang

Reviewer’s report:

This Manuscript reported association of XPD gene polymorphisms and hepatocellular carcinoma (HCC) risk in a hospital based case-control study in Guangxi, China. Previous studies have proved several environmental risk factors associated with HCC risks in this area, including dietary aflatoxin exposure and chronic HBV infection. The individual susceptibility, such as genetic polymorphism in DNA repair genes, in this population is of research interest in the field. In this study, genetic polymorphisms of XPD gene codon 312 and 715 and aflatoxin exposure status was analyzed and the interaction between aflatoxin exposure and XPD gene polymorphisms was concluded. Questions for this manuscript are the accuracy and validity of methods used for measuring aflatoxin exposure and determining the aflatoxin exposure years. Authors claimed that they adapted an ELISA to measure AFB-DNA adduct in peripheral blood DNA, which was never been validated and reported by the original authors and their published paper (Hsieh LL et al. Cancer Research 48:6328-6331, 1988). Original paper only measured DNA from liver and kidney tissues in treated animals and human patients. The method may never work for measuring AF-DNA in human peripheral blood if using the procedure as authors described. How can a volume of 4 mL whole blood generate 50 microgram DNA? What are the critical steps of purification and concentration of AFB-DNA adduct from DNA, which are essential for the measurement? These need to be clarified before considering for publication.

Specific comments:

1. In method section, authors need to explain more in detail about the basis of definition of AFB1-exposure years? What is the relationship between AFB1-exposure years and ages of study subjects?

2. The median value of AFB1-exposure years in case and control group is 40 and 48 years, respectively. Is AFB1-exposure years significantly different between case and control groups? If it is significant, what is the reason for using this criterion?

3. Authors should describe in detail for the method to measure AFB1-DNA adducts level in DNA samples, including list the source of monoclonal antibody and AFB1-DNA standard.

4. According to the original publication, the method authors used to measure
AFB1-DNA adduct, was carried out in tissue or placental DNA samples. Is there any evidence to indicate or validate AFB-FAPy as a reliable biomarker of AFB1 exposure using DNA generated from peripheral blood leucocytes samples?

5. In table 2, authors compared the AFB1 exposure year and levels in case and control groups. The comparison was based on the grouped data, not the original continuous variables. Why not using the original AFB1 exposure year and AFB1-DNA adduct value to do the comparison, which can provide more information. Authors should provide the detectable rate of AFB1-DNA adduct and levels using the box-plot in case and control groups.

6. In table 2 and 5, Authors need to explain why the adjusted OR statistically change so dramatic as compared to crude OR.

7. As stated in result section, “interestingly, we found that the interaction between genotypes and AFB1-exposure years can modify the main effects of XPD codon 751 genotypes in the multiplicative model”. Logically, there should be no interaction between XPD genotype and AFB1-exposure years. Please explain what the interaction means here, or reason to introduce the interaction into the model.

**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.