Reviewer's report

Title: Whole genome methylation array analysis reveals new aspects in Balkan Endemic Nephropathy etiology

Version: 6 Date: 22 July 2013

Reviewer: Eoin Brennan

Reviewer's report:

Thank you for the opportunity to review the Authors' responses to my Revision suggestions. Please see my responses to individual comments below, plus additional minor comments.

Author Comment 1: "We cannot perform gene expression analysis since we do not have RNA. We have only DNA samples which are obtained between 2003 and 2011 and new sample collection will take a lot of time. That is why we will perform methylation specific high resolution melting curve analysis to validate our data. This proposal for expression analysis is very valuable and in the future we will apply for a new project."

Response: It is disappointing that the authors cannot investigate the functional relevance of hypomethylation at the top 3 genes by measuring gene expression, as this would be strong addition to the manuscript. However, as the authors explain, they presently have no RNA to perform such gene expression analysis.

Author Comment 2: "In relation to pathway analyses of the genes associated with differently methylated CpG islands in table 2 and 3. We performed basic pathway analysis and the major pathways are discussed"

Response (Major Compulsory Revision): The authors have now performed pathway analysis as outlined in Figure 2. The authors should provide information in the methods on how the pathway analysis was performed, software used, p-value cut-off for significantly enriched pathways in the DMRs. It would also be good to include this information as a Supplemental table with the p-values provided.

Author Comment 3: "The data for the patients included in the pools is extended with the addition of the most relevant clinical parameters. The required information is provided as excel tables"

Response: This is now addressed.

Author Comment 5: "We took in consideration the remarks concerning the discussion section”

Response: This is now addressed.
Author Comment 6: "Grammatical and typographical errors are corrected. The manuscript is revised by native English speaker"

Response: Thank you. This is now addressed.

ADDITIONAL Minor Essential Revisions:

1. The line in the Background section "CpG island methylation is involved physiologically in..." has different font to rest of text.

2. Full titles are needed for each of the Supplemental Tables, and also at the top of the excel file so when readers access the tables they can follow clearly what they are looking at. The word "###############" is used throughout these tables, please translate to English. The supplemental tables need to be mentioned also in the main text of the paper in the results section.

3. "Table" and "Tab" are used in the manuscript. Please change "Tab" to "Table"

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

**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