Reviewer’s report

Title: Generation of a strand-specific, genomic tiling array of the human Major Histocompatibility Complex (MHC) and its application for DNA methylation analysis.

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Reviewer: Elisabeth Weiss

Reviewer’s report:

The authors have generated a genomic tiling array of 2 kb resolution covering the whole HLA region. This array can be used for different applications for studying the expression and epigenomics of the human MHC. The authors demonstrate its usage for DNA methylation profiling and identify further characterise tissue-specific differentially methylated regions (tDMRs). This array will be useful for many groups as HLA-genes have an important role in complex diseases including neoplasia.

Minor Essential Revisions:

The titles says that the manuscript describes a strand-specific genomic tiling array, although no data are shown which demonstrate strand-specificity, thus this should be omitted from the title

p. 13 first paragraph (Figure 2): The authors do not comment on the obvious low methylation observed for the class II region.

p. 13, second paragraph and Figure 3a: The spacing (steps of 5?) of the columns is not clear to me. If 9 % of the probes are repeat-free (= repeats 0 %) the 12-% column would be at 95 %, the text says 12 % consist of repeat sequences only (=100%).

Figure 5: The authors claim that they randomly chose six tDMRs to subject them to independent methylation analysis using bisulphide sequencing. The chromosome 6 coordinates are given in the legend to Figure 5. This is a region contains no known gene. The authors should give the location of the analysed region within the HLA-complex and its relevance.

Table 2 and Figure 7: The authors speak of the complement region, when they mean the C4 genes (C4A and C4B). This is confusing. The 18 tDMRs 14 to 30 and 12 map to the C4 genes. But I count 21 tDMRs (vertical black line) in Figure 7 within the complement region and also tDMRs in Table 2 map to the complement genes, which include C2. If the authors count differently, they should mark or the surrounding the vertical black lines representing the tDMR mapping to the complement region.

The authors concentrate in their final experiments on the complement C4 genes.
This is a highly polymorphic region with regard to gene number, as two to seven C4 genes may be present in a diploid human genome. In the discussion they state the copy number variation but do not discuss whether the tissue and cell types used in this study differ with regard to the C4 gene set. The C4 gene content of DNAs analysed should be known. If the C4 gene number is the same in all DNAs, the authors should state this. Otherwise they should discuss whether different gene numbers would affect their results.

**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 interest.