In this manuscript, Dr. Kurushima and colleagues conducted comprehensive two-stages epigenetic-based association study to periodontitis based on hm450 array from UK twins cohort. Both gingival bleeding (N=528) and tooth mobility (N=492) were investigated in the study and several positive association were identified, such as *ZNF804A*, *IQCE* and *XKR6. T*he study was performed rigorously and the findings are interesting. I have several concern for the authors to think about again and make further response.

**Major Compulsory Revisions**

1, A schematic overview or graphical abstract of the study was encouraged to be provided as the Figure 1, including the sample, analysis pipeline and main idea and found of the study.

2, The authors captured 27 previously reported CMT disease-causing genes. It is a great strategy to identify the disease related mutations, however, is there any possibility to ignore some important unknown targets which might have not been reported in previous studies. Meanwhile, how to make sure this mutation (c.44G>A) is the unique and only disease-causing genes for this family? Is there any possibility the disease is caused by the interaction between with any other genes?

3, As the author mentioned in the manuscript, the diagnosis of CMT is mainly based on patient’s clinical characteristics, electrophysiology and neuropathology characteristics, then did the genetic analysis result is consistent with the clinical characteristics for the main patients in this family should be discussed.

4, The authors also mentioned they actually captured another 179 genes, however, these gene list were never shown in the manuscript? Why? These totally gene list should be provided as the supplementary table.

5, Although the authors give explicit description for the distribution of the c.44G>A in the members of the family. However, the authors didn’t show the segregation analysis method and the result? Why not provide the P-value?

6, Availability of data and materials is another problem. The datasets supporting the conclusions of this study, especially the sequencing data should be provided in corresponding database (Chinese database or GEO) to make sure the result is reproducible.

The authors mentioned personalized treatments and prevention in both abstract and background, however, nothing further discussion were provided to illustrate how to apply methylation signals in ‘personalized treatments and prevention’.

The authors tried to validation the result from whole blood in buccal and adipose tissues, However, as known, the methylation pattern in different tissues usually is different, what’s the meaning to validate the result in different tissue for periodontitis.

I want to know why gingival bleeding status and tooth mobility status were obtained from different samples?

The author mentioned ‘Informed consent was obtained from all participants before sample and data collection’. As we known, UK twin cohort blood extraction is far before the further study design, a detail relationship about current study design and blood sample, as well questionnaire will be helpful.

In the self-reported questionnaire section, I am wondering why not ask the earliest time for the tooth mobility? Or why not ask the times of the gingival bleeding in the past several years?

**Minor Essential Revisions**

1, For the Figure 2, it is only a data quality control to show the good coverage of sequencing. It should not be taken as the main figure, please move it to the supplementary or make this figure as the sub-figure.

2, For the Table 1 and Table 2, why not combine them together? I think the information are quite similar and should be shown in a unique table so that the reader could identify the features more quickly. Meanwhile, comprehensive clinical, epidemiological information should be summarized, such as age, smoking, drinking, and attached as the supplementary tables. It is recommended to put some visual pictures for the disease and as I mentioned before, an elaborate schematic overview could be prepared.

3, Line 135 to line 146 could be summarized in the Figure 1 and please make sure to label the important numbers such as sample size and all the exact numbers involved in this study and the method which are applied for the genetic or bioinformatics analysis.

4, I don’t know why authors only provided the proband and her father’s data and information in the manuscript, such as Table 1,2 and Figure 3. Why ignore the other data? I think all these result should be provided even as the supplementary.

**Discretionary Revisions**

1, The manuscript should be editor and build further, the current version is full of non-related redundant materials which are not related to the main-point of the study aim. Meanwhile, some of important information are lost. I recommend the authors could make the manuscript more compact.