Comments to the Authors,

This manuscript studied the genetic and epigenetic alterations of Netrin-1 receptors in gastric cancer with chromosomal instability in a Japanese population. In the present study, LOH, DNA methylation, gene expression and chromosomal instability of two genes: *DCC* and *UNC5C* were measured and then the associations between them were conducted. The study was performed rigorously and the findings are interesting. However, the manuscript needs more careful editing and it should be more concise with the usage of tables and figures rather than descript the numbers with long sentences. In general, I'd recommend publication if the authors can address the following concerns and prepare a more concise draft.

**Major Compulsory Revisions**

1, In the first paragraph of background, what’s the accurate proportion of the infection rate for H.pylori in gastric cancer patients?

2, In the revised manuscript, the accurate number or scale should be provided among the manuscript rather than small proportion, frequently or/and majority, etc.

3, Please provide the relationship between MSI and cancers, as well as the clinical significance of MSI, CIN in the background.

4, Please provide the frequencies of the decreased expression of DCC in previous literature reports?

5, Is there any significant association among MSI, CIN, mutations and DNA methylation?

6, In the result 3, please provide the biological or clinical importance and biological interpretation of the significant association between LOH of 18q locus and CIN phenotype.

7, How many alternative splicing of DCC and UNC5C? Is it enough to estimate the gene expression to these two genes with only one RT-PCR primers?

8, Please provide the accurate location for the primers of RT-PCR, LOH probes with figure or genomic position.

9, In the result 2, 1.0% and 5% were set as the threshold of positive methylation status. Is there any significant difference for the result or conclusion if other values were selected? Can you provide the changing-curve of the methylation positive frequency for cancer and normal tissues along with the different threshold?

10, In the result 8, please provide patients number of LOH positive if the criterion was set as with one, two and three microsatellite markers.

11, In the result 10, please provide the statistical method how to get the p-value of 0.007.

12, In the result 10 and table 3, the percentage of the UNC5C aberrant in IV (18%) is not larger than III (48%). How to get the conclusion: *UNC5C* alterations gradually increased according to the progression of the TNM stage.

13, Figure 4 should be presented as the point-line figure rather than histogram, which is clearer to the readers.

**Minor Essential Revisions**

1, It would be better to introduce the biological relevance of netrin-1 and its receptors in the beginning of the background.

2, Figure 1 is useless and less-information. Please replace Figure 1 with supplementary Table 1.

3, In the result 7, I think “Figure 3B” should be replaced with “Figure 3D” and “Figure 4D” should be replaced with “Figure 3D”. Here, please provide some previous evidences, literatures or gene expression microarray data to validation your result. It would be better to validate the result with BSP and real-time PCR.

4, In the line 10-11 of discussion section, 13, 25, 30 and 11 were not found in the table 3.

5, In the abstract section. It seems only alteration UNC5C continues to escalate in both receptors with the progress of the disease, isn’t it?

**Discretionary Revisions**

1, In the second and third paragraph of background, please provide the precise proportion for the LOH of 18q21 from previous literatures.