Reviewer's report

Title: Comprehensive analysis of human microRNA target networks

Version: 1  Date: 6 December 2010

Reviewer: Ju Han Kim

Reviewer's report:

Major Compulsory Revisions

The central question of the authors is whether a set of miRNA target genes regulated by a particular miRNA constitute the biological network of functionally-associated molecules or simply reflect a random set of functionally-independent genes.

It seems, however to my best knowledge, that this question has already been answered by many other works. Dang et al. (Seminars in Cancer Biology, 2006, 16, 253–264) reported c-Myc regulate genes that are functionally related using many high-throughput screens based on microarray gene expression profiling, SAGE, ChiP. Lall et al. (Current Biology, 2006, 16, 460–471) showed a number of nematode miRNAs regulate biological processes by targeting functionally related genes from GO term analysis. Wang et al. (Bioinformatics, 2010, vol. 26 no. 13, 1644–1650) inferred the pairwise functional similarity and functional network for human miRNAs by measuring the similarity of miRNA-associated disease directed acyclic graph. Jiang et al. (BMC Systems Biology, 2010, 4(Suppl 1):S2) constructed a functionally related microRNA network based on the overlap between their target genes and measured the functional relatedness between two miRNAs. In addition to these papers, there are numerous papers which have addressed the question that a set of miRNA target genes regulated by a particular miRNA constitute the biological network of functionally-associated molecules.

It seems that the central question of the manuscript has been well answered and it is not clear what it adds.

In pages 6 and 7, the numbers for pathways/diseases/pathologic events may be incorrect as compared with Supplementary Table 1 which shows all the information on 232 miRNAs. The table below is reconstructed by the sentence “top three pathways, diseases, and pathological events were individually totalized” in the pages. The total number is supposed to be from 696 (=232*3), since each column has 232 miRNAs and top three are added. The sums 39, 24, 68 should be checked.

<table>
<thead>
<tr>
<th>Function</th>
<th>1st Rank</th>
<th>2nd Rank</th>
<th>3rd Rank</th>
<th>Sum</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>transcriptional regulation by RB/E2F</td>
<td>33</td>
<td>5</td>
<td>1</td>
<td>39</td>
<td>39/696*100 = 5.6</td>
</tr>
<tr>
<td>transcriptional regulation by POU domain factor</td>
<td>7</td>
<td>5</td>
<td>12</td>
<td>24</td>
<td>24/696*100 = 3.44</td>
</tr>
</tbody>
</table>
Some references may help readers to understand it better. The reference in Proteomics, 8, 1975-1979, 2008 may be helpful.

Minor Essential Revisions
1. The biological meaning of the concept of "canonical network" is not well described in the manuscript.
2. It needs to indicate the proportion of target genes regulated by a particular miRNAs belong to pathways/diseases/pathologic events.
3. Although the present study used KeyMolnet in order to characterize molecular networks of targets of miRNAs, it is necessary to show simple descriptions about the network, such as how to calculate edges and information source of KeyMolnet.
4. In Fig 1(b), the end of the title and the Y axis label were cut off.

Level of interest: Reject as not of sufficient priority to merit publishing in this journal

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.