Reviewer’s report

Title: A novel mutation in H/ACA box of telomerase RNA component gene (TERC) in a young patient with myelodysplastic syndrome

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Reviewer: Tara Beattie

Reviewer’s report:

In this short but informative manuscript the authors identify a novel mutation in the RNA component of human telomerase that was found in a young man with MDS. This is the first report of a mutation in the H/ACA box of hTR in MDS. The authors also demonstrate that the same heterozygous mutation was found in the patients father and the grandmother dies from bone marrow failure. This is all consistent with a germine mutation in the TERC gene contributing to the disease.

Figure 1 illustrates a schematic of hTR and identifies where in the secondary structure the mutation occurs. It is not obvious with this specific A to G mutation would result in shortened telomeres, however it is know that this region of hTR is critical to RNA accumulation. Figure 2 nicely demonstrates telomere length as a function of age with telomere length data generated using a qPCR technique. It also nicely demonstrates that both the telomeres of the patient and of his father are shorter than age matched controls in peripheral blood. Figure 3 uses the STELA assay to examine telomere length on specific chromosomes and again shows shortened telomeres in the MDS patient harbouring this mutation. And finally Figure 4 shows decrease telomerase activity in VA13 cells expressing hTERT and either WT or mutant TERC.

Compulsory Revisions:

The work that the authors have done is very nice and is the beginning of a very interesting study, however there are a number of additional experiments that would greatly enhance this study. Since the authors have access to patient samples it would be nice to see telomerase activity from the actual blood samples that the telomere length analysis was done. In addition, since this region of the molecule is known to affect the stability and accumulation of hTR and well as interaction with the protein dyskerin, it would be nice to include these studies as well (ideally in the patient samples). Since it is also postulated that this region is not necessary for telomerase activity per se and that mutations in the H/ACA box still retain the ability to bind to hTERT, inclusion of these experiments would also be interesting.

Minor Revisions:

On minor comment in the abstract, I don’t believe the authors can conclude from these studies that the mutation in TERC was responsible for the bone marrow failure….It correlates with and is consistent with , but the data does not address
cause of the disease.

**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 interests