Review Date: 2019-06-17 16:03

Specific Comments To Authors: Authors have described a novel frameshift mutation in the TBG protein leading to complete thyroxine-binding globulin deficiency. As a clinical case it explains why genome sequencing is important to address certain clinical cases. Instead of sequencing only a segment of TBG gene, complete gene should have been sequenced. The case report submitted by Dang et al. discusses a novel frameshift mutation in the TBG protein leading to complete thyroxine-binding globulin deficiency. There are certain clarifications and changes required as mentioned below. Upon satisfactory response this manuscript may be accepted.

1. You have provided the details of instruments used in the material and method section only. Provide the details of all kits used for different estimations in the methodology section also.

Response: Thank the reviewer for pointing this out. We have added the details of all kits in the Methods in the revised paper.

2. It is clear that due to the loss of thyroxine binding sites in the truncated protein there is reduction in TT3 and TT4 levels, but the truncated protein (with first 134 amino acids) should have been detected by the kit since this mutation is not leading to complete abolishment of protein synthesis as reported in earlier literature for other mutations. Is it due to no secretion or due to the possibility that antibody which is used in the kit to detects TBG protein binds in the truncated region for detection, hence no detection of TBG at all. <3.5 ug/ml seems like a speculation only, where the truncated remains if it is not secreted into blood. Provide satisfactory explanations in the discussion section.

Response: Thank the reviewer for pointing this out. We have added the explanations in the discussions in the revised paper. “However, the mechanism for the failure to detect immunoreactive TBG in the serum of these patients harboring this mutation remains unknown. We speculated that three reasons may be concerned. The first one may be the impaired synthesis of the truncated TBG proteins. The 19-nucleotide insertion in exon 1 is supposed to affect the transcription or the translation of TBG, leading to the failure of synthesis of mutant TBG. The second one may be the impaired secretion of the truncated TBG proteins. Most of the truncated TBG molecules previously reported were not secreted [20-22]. They remained in the rough endoplasmic reticulum and rapidly degraded within the cells, or had impaired intracellular transport in the blood. And the last reason may be associated with the TBG antibodies used in the present study, which can only bind in the truncated region, but not in the non-truncated region, hence results in no detection of serum TBG.”

3. In line 210 you have used the word “mutation” along with “TBG-Poly (L283F)” which is technically incorrect. L283F is polymorphism so remove the word mutation.

Response: Thank the reviewer for pointing this out. We have removed the word mutation in the revised paper.

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor rev