Dear Reviewers,

Thank you for reviewing our manuscript entitled 'Clinical manifestations of adult hereditary spherocytosis with novel SPTB gene mutations and hyperjaundice: A case report'. We appreciate your constructive comments and have revised and strengthened the manuscript based on the suggestions. We attach the revised version for your consideration. In addition, we have provided a point-by-point response to the reviewers' comments below.

Reviewer #1:

• In the case summary (Page 2) it is advised to add the source of DNA i.e., either blood or tissue. Also, the genotype of the variant (heterozygous or homozygous) needs to be given.

We thank the reviewer for these helpful comments. The source of DNA is blood and the variant genotype is heterozygous. These two pieces of information have been included in the revised manuscript.

• It is surprising that the variant was not seen in the parents. The authors should clarify whether they are the biological parents. Has adoption been ruled out? If so that needs to be mentioned. Have the authors confirmed the variant by drawing an independent blood sample?

The patient's parents are his biological parents; we have included this information in the revised manuscript. When the variant was found in the patient, we took blood samples to verify that there were no similar variants in the blood of his parents.

• The authors in the introduction mention that HS is an autosomal recessive hereditary disease. However, they have identified a heterozygous variant in the SPTB gene (c.1801C>T). How do they justify the causal role of the variant?

We are grateful to the reviewer for pointing out our mistake here. Most cases of HS (about 75%) are actually inherited by an autosomal dominant pattern, although autosomal recessive inheritance and de novo mutation have been described in a subset of patients. We have made changes in the manuscript accordingly.

• In personal and family History (Page 4), although the personal history of the patient is given no mention as to any other family members being affected is not mentioned.

There was no similar performance among the family members of the patient; we have revised the article to reflect this.

• Under Physical examination, have the authors collected the Waist circumference and Hip circumference?

The patient's waist circumference and hip circumference are 90 cm and 93 cm, respectively, and we have included this information in the revised manuscript for clarity.

• Although the authors mention that "High-throughput sequencing of a liver panel" on Page 5, there is no mention of the panel they have used, the genes they have screened. It would be beneficial to mention the liver panel genes and the platform for the high through-put sequencing that was used (Illumina/Ion torrent).

We thank the reviewer for these helpful comments. The sample used a whole exome sequencing probe to analyze 228 genes associated with liver affected diseases, including a liver panel. The capture probe is customized from IDT. Illumina Novaseq 6000 second-generation sequencing instrument was used for sequencing detection.

• Were any other variants identified in the patient? Any VUS variants

identified? The rsID for the identified variant should be given.

Two genetic testing institutions were selected for the genetic examination of the patient, and the *SPTB* mutation site was the variant identified by both institutions. Another genetic variation reported at one of the testing facilities is that on chromosome 9(chr9:104125045), the *BAAT* gene in exon 9 contained a mutation of cytosine to thymine at nucleotide 922, resulting in a glutamine (Gln) nonsense mutation at amino acid 308 to a stop codon [NM_001701.4: c.922C>T(p.Gln308*)]. After searching literature, we believe that this second variant is not a pathogenic gene, so it is not described in the article. And this variation was not found to be included in dbSNP database, that is, there was no rs number.

• It is preferable to call the changes in DNA as variants rather than mutation.

We thank the reviewer for this helpful comment. We have modified the manuscript accordingly.

• The authors mention that high-through put sequencing was used to identify the variant. However, electropherogram (Sanger's sequencing) is given. This is leading to confusion. In case they have validated the variant that was identified in the high through put sequencing by Sanger's sequencing they need to mention this. Was high through put sequencing done in all the family members or only the identified variant was screened?

We are grateful to the reviewer for highlighting this issue. The variant that was identified in the high-throughput sequencing was validated by Sanger sequencing. We have clarified this in the revised manuscript to avoid any possible confusion. The patient's parents were screened for the identified variant, and his daughter was screened for all genes. Neither the parents nor the daughter of the patient had any variant genes.

Reviewer #2:

My concern is why cholecystectomy was not done during splenectomy which is commonly carried out in Heriditary spherocytosis with gallstones.

We thank Reviewer 2 for reviewing the manuscript and raising this question. The endoscopic retrograde cholangiopancreatography with sphincterotomy + balloon exploration and lithotomy + biliary stent angioplasty were performed before splenectomy to treat the patient's biliary obstruction and biliary calculi. Later, we rechecked MRCP and found no calculi in the biliary tract and gallbladder; therefore, the gallbladder was not resected during splenectomy.