Thank you for the reviewers and editor' comments concerning our manuscript, these comments are all valuable and very helpful for reviewing and improving our paper. We have studied comments carefully and have made revisions, we hope our revisions will meet with your approval. The main corrections in the paper and the response to the reviewers and editor's comments are as below:

Reviewer #1: 1. How many cases of jaundice were seen during the period? 2. What was the line during which the cases were selected for analysis? 3. Were the cases chosen based on the associated conditions? 4. How was the cost of the genetic sequencing met? 5. How did the next generation sequencing influence further management in the cases? 6. Can the randomly 5 cases be representative of all cases of jaundice for association of genetic factors? 7. Based on the manuscript can a routine genetic testing be carried out for all cases of 'severe jaundice'?

Responses:

Question 1,2,3.

This article was based on a retrospective study, the subjects were full-term neonates (age≥35 weeks, birth weight≥2500g), admitted to our hospital from Dec 2014 to Dec 2019, neonates with serious diseases and major birth defects were excluded. A total of 117 cases with hyperbilirubinemia were collected, and NGS was performed. Among these cases, we selected five representative cases with extremely severe hyperbilirubinemia as a case report (this part of the description has been added in the first paragraph of case presentation).

4. The cost of the genetic sequencing was free for neonates, and was supported by funds (Natural Science Foundation of Guangdong Province 2016A030307035 and Medical Research Foundation of Guangdong Province A2018233).

5. The neonatal samples didn't receive NGS when they were in hospital at the stage of neonates, NGS was performed several years later after they were discharged from our hospital. Five children were clinically followed-up at about 4 years old, their intelligence and development were normal (described in the last paragraph of case presentation and the third paragraph of conclusion).Therefore, next generation sequencing did not influence the management in the cases.

6. 5 cases were selected based on their clinical manifestation, they could not be representative of all cases of jaundice for association of genetic factors.

7. We proposed at last, genetic detection should be considered for the early diagnosis of severe hyperbilirubinemia in neonates (described in the last paragraph of conclusion).

Reviewer #2: By retrospectively studying five neonates with severe hyperbilirubinemia, the authors conclude that genetic variants may play an important role in an increased risk of neonatal hyperbilirubinemia, and severe jaundice in neonates may be related to a cumulative effect of genetic variants. This manuscript is a good example for that genetic detection should be considered for the early diagnosis of severe hyperbilirubinemia in neonates. I have three suggestions. 1. Articles of the references were published in or before 2018, excepted for reference 16 (in 2020). It will be better if more articles published in recent three years are mentioned. 2. Line 272: Please insert "16" before the authors' name. 3. For patient 5: Born at 35+4 weeks of gestation plus heterozygous for the UGT1A1 c.G211A (p.G71R) mutation seems not sufficient to manifest severe hyperbilirubinemia (total bilirubin value = 584.40 μmol/L) at age of 7 d. Because seven variants, c.211G>A, g.-3279T>G, the number of CAT and TA repeats

in UGT1A1 gene promoter, c.686C>A, c.1091C>T and c.1456T>G have been determined for the patient, other UGT1A1 gene variants should be concerned. The best way is to determine full-length UGT1A1 gene.

Responses:

1. Articles of the references (2-5, 9-12) have been replaced by those published in recent years.
2. We have inserted "16" before the authors' name in reference 16 for this oversight.
3. In our experiment, targeted NGS was performed for patient's DNA, the sequencing region included all exons and adjacent introns of UGT1A1, we didn't find any mutations other than c.211 G>A in this patient.

Science editor:

The aim of this study was to identify gene variants affecting bilirubin levels in five representative patients by next-generation sequencing (NGS). There are many influencing factors of jaundice. Whether the five randomly selected cases can represent all jaundice cases related to genetic factors, are there too few patients. In addition, in "CASE PRESENTATION" section, it is suggested that chief complaints, history of present illness, history of past illness, personal and family history, physical examination, laboratory examinations, and imaging examinations should be described under a corresponding subheading according to the journal's requirements.

Language Quality: Grade B (Minor language polishing)

Scientific Quality: Grade C (Good)

Responses:

5 cases were selected based on their clinical appearances, they could not represent all jaundice cases related to genetic factors, but they might imply the most important genetic factors for unexplained neonatal jaundice, the main genes such as UGT1A1, G6PD and EPB41 were identified in this series of cases.

The chief complaints, history of present illness, personal and family history, physical examination, laboratory examinations, and imaging examinations were added in the revised manuscript.

Once again, thank you very much for your comments and suggestions.