Peer Review File

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Reviewer A

Comment 1: Line 1, 17, 58, 342 and 343: CHD7 □ CHD7 - review all text.
Reply 1: We are extremely grateful to reviewer for pointing out this problem. We check through the manuscript and changed all *CHD7* gene into italic font (see Page1, line3, 18, Page 4, line 77-78 and Page 15, line 685).
Changes in the text: We changed *CHD7* into italic style. Please see Page 1, line 3, 18; Page 4, line 77-78 and Page 15, line 685.

Comment 2: Line 28: spice or splice?
Reply 2: Thank you for your valuable comment. We 've corrected the typo. We used RT-PCR and Sanger sequencing to investigate the influence of a splice variant (see Page 3, line 54).
Changes in the text: We corrected the typo of spice into splice. Please see Page 3, line 54.

Comment 3: Line 44 and 53: Missed “.”
Reply 3: We are very grateful to your comments for the manuscript. We 've added the end mark (Page 3, line 67 and Page4, line 77-78).
Changes in the text: We added the end mark in the text. Please see Page 3, line 67 and Page4, line 77-78.

Comment 4: Line 71: I suggest including the identification in OMIM
Reply 4: Thank you for your valuable suggestion. We 've added the OMIM code of CHARGE syndrome in the text (see Page 5, line 89-90).
Changes in the text: We added the OMIM identification code of CHARGE syndrome (214800) in the text. Please see Page 5, line 89-90.

Comment 5: I suggest shortening the second and third paragraphs of the introduction. The contextualization of the subject can be brief.
Reply 5: We are very grateful to your comments for the manuscript. We’ ve combined the second and third paragraphs of the introduction into one paragraph, refining the contextualization of CHD genetic etiology. (see Page 5, line 94-108).
Changes in the text: We refined the description in the introduction of CHD genetic etiology. Please see Page 5, line 94-108.

Comment 6: I suggest adding length and head circumference at birth in case reports.
Reply 6: Thank you for your generous comment. We did history search on our medical history system and found the record of length (45 cm) and head circumference (34 cm) in proband of

family #2 (see Page 9, line 530-531). However, other patients were not referred to our hospital immediately after birth and record of their length and head circumference at birth remain unclear.
Changes in the text: We added record of length and head circumference of proband in family #2. Please see Page 9, line 530-531.

Comment 7: Line 185 and 209: Remove “that the patient had”.
Reply 7: We are very grateful to reviewer for pointing out this problem. We have deleted the expression “that the patient had” in the text (see Page 9, line 520; Page 10, line 550)
Changes in the text: We added record of length and head circumference of patient 2. Please see Page 9, line 520; Page 10, line 550.

Comment 8: Line 218: “cartilage .” to “cartilage.”
Reply 8: Thank you for pointing out this typo. We have changed “cartilage .” to “cartilage.” in the corresponding text. (see Page 10, line 557)
Changes in the text: We changed “cartilage .” to “cartilage.” in the text. Please see Page 10, line 557.

Comment 9: Line 223: At 10 months of age it is difficult to refer mental retardation, perhaps it would be better to refer developmental delay.
Reply 9: Thanks for your comment of the manuscript. We’ve changed the description of “mental retardation” into “developmental delay”, which is more suitable to the situation for patient at the age of 10 months (see Page 10, line 560).
Changes in the text: We changed “mental retardation” to “developmental delay” in the text. Please see Page 10, line 560.

Comment 10: Lines 327-329: I suggest deleting the expression. “, which is a rare genetic disease characterized by multiple congenital abnormalities, including congenital heart defect, coloboma of the eye, atresia of the choanae, retardation of development, genital anomalies, and ear anomalies/deafness.” It has already been described above.
Reply 10: Thank you for your generous comment. We deleted the additional description of CHARGE syndrome which is already been mentioned in introduction. (see Page 14, line 668).
Changes in the text: We deleted the expression. “, which is a rare genetic disease characterized by multiple congenital abnormalities, including congenital heart defect, coloboma of the eye, atresia of the choanae, retardation of development, genital anomalies, and ear anomalies/deafness.” in the text. Please see Page 14, line 668.

Comment 11: In Table 2, I suggest deleting yes and no. Put in place of “yes”, "+", and in place of “no”, leave it unfilled.
Reply 11: We are extremely grateful for your comment on the manuscript. We checked the

clinical characters of 4 probands, filling Table 2 with "+" or detailed symptom while leaving the other place unfilled. (see Page 19, line 812-814).
Changes in the text: We refilled the Table 2 with detailed clinical characters. Please see Page 19, line 812-814.

Comment 12: I liked the detailed clinical description of the patients, the tables and the images.
Reply 12: Thank you for your generous comment. We've added some details of clinical description of patients in the text (see Page 8, line 516 to Page 10, line 565). Tables of clinical characters was also updated with detailed description in Table 2 (see Page 19, line 812-814). Images of echocardiography of patients were added into Figure 1 (see Page 22, line 832-840).
Changes in the text: We added details of clinical description of patients in the results. Please see Page 8, line 516 to Page 10, line 565. We refilled the Table 2 with detailed clinical information. Please see Page 19, line 812-814. We added several images of echocardiography into Figure 1. Please see Page 22, line 832-840.

Reviewer B

Comment: Please check if more references should be cited in the following sentence since you mentioned "studies":

- A series of studies showed that the incidence of CHD was higher in patients with CHD7 mutations (66%–92%) than in patients without CHD7 mutations (71%)(21).

Reply: Thank you for your valuable suggestion. We added 3 references (reference 25-27) to the text (see Page16, line 363; Page 21, line 489-496).
Changes in the text: We added corresponding references. Please see Page16, line 363; Page 21, line 489-496.

Comment: Figures and Tables

- Please provide the description of B in Table 4.
- There is no T, P, D in Table 3. Please check and revise.
- All abbreviations in tables/figures and their legends should be defined, e.g. CHD, RA, LA etc. in Figure 1. Please check all tables and figures.

Reply: Thank you for your valuable suggestion. We rewrote definitions of abbreviations in the Table3, Table4 and Figure1. (see Page23, line 525 to Page24, line 553)
Changes in the text: We revised some definitions of abbreviations. Please see Page23, line 525 to Page24, line 553.

Comment: Please provide the full name of CAMS in the Acknowledgments.
Reply: Thank you for your valuable comment. CAMS is the abbreviation for Chinese Academy of Medical Sciences. We added the full name of CAMS in the Acknowledgments (see Page18, line 398-399).
Changes in the text: We added the full name of CAMS in the Acknowledgments. Please see

Page18, line 398-399.