

Peer Review File

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First external peer review

Replies to comments from reviewer A

Comment 1: The gene responsible has been renamed to ADA2 from CECR1. Please edit that section to include "formally known as CECR1" and change the CECR1 mentions throughout the text to ADA2.

Reply1: Thank you for correcting my inaccurate description. I have revised "CECR1" as "ADA2" throughout the text, and **the changes are marked in red in the text.**

Changes in the text: see Page 1, line 2 and 19; Page 2, line 33, 40 and 47; Page 5, line 118 and 120; Page 7, line 159 and 168; Page 9, line 204; Page 13, line 306 and 308.

Comment 2: During the section where the diagnosis of systemic juvenile arthritis (SJA) was made, mention of the ILAR criteria and whether it was fulfilled or not would be nice to include so that readers could see how the SJA diagnosis was made.

Reply 2: I have added information regarding the ILRA classification criteria for sJIA (Edmonton 2001, revised version) as advised; **the changes are marked in red in the text.**

Changes in the text: see Page 4, line 79 to 83.

Comment 3: Some discussion as to why CT angio may be "normal" would also be beneficial as the involved vessels in DADA2 are so small that CT and MR angios are not always sensitive enough to identify these affected vessels.

Reply 3: According to your comment, I have added discussion as to why CT angiography may be "normal"; **the changes are marked in red in the text.**

Changes in the text: see Page 6, line 150; Page 7 line 151 to 152.

Comment 4: It would be important to really highlight that tocilizumab, although good at controlling the inflammatory markers/fevers/etc HAS NOT been effective in preventing ischemic/hemorrhagic events (GI perf in this patient, hemorrhagic stroke (PMID: 29936104) and ischemic stroke in another publication (PMID: 30610243). This is important for treating physicians to realize and, you only mention how there was a successfully treated Castleman's/DADA2 patient with tocilizumab.

Reply 4: I have highlighted the limitations of the tocilizumab in DADA2 as advised, and **the changes are marked in red in the text.**

Changes in the text: see Page 8, line 181 to 185.

Comment 5: Line 109: Qing Zhou's name is reversed.

Reply 5: I have corrected Professor Qing Zhou's name; **the change is marked in red**

in the text.

Changes in the text: see Page 5, line 121.

Replies to comments from reviewer B

Comment 6: Only one minor concern, the authors may want to clarify “a small boy” means “a little boy (young boy in terms of age)” or “a boy who is small in size (height and weight)”.

Reply 6: To avoid ambiguity and obscurity, I have revised “a small boy” to “a 3-year-old boy.” **The changes are marked in green in the text.**

Changes in the text: see Page 1, line 25; Page 2, line 27; Page 3, line 53.

Replies to comments from reviewer C

Comment 7: Lines 19, 47, 182 – CERC1 is the old term for it. This should be changed to “bi-allelic loss-of-function mutations in the ADA2 gene (formerly known as Cat Eye Syndrome 1; CERC1)”

Reply 7: I have changed “*CECRI*” to “*ADA2*” as advised. Because this concern is similar to one of the Reviewer A’s concerns, **the revised section are marked in red or blue.**

Changes in the text: see Page 1, line 2 and 19; Page 2, line 33, 40 and 47; Page 5, line 118 and 120; Page 7, line 159 and 168; Page 9, line 204; Page 13, line 306 and 308.

Comment 8: Line 23 – Diversity of clinical presentation (remove the s as it does not need to be plural)

Reply 8: I have changed “presentations” to “presentation,” **and the change is marked in blue in the text.**

Changes in the text: see Page 1, line 23.

Comment 9: Line 35 and 129 – The term ‘protean’ is not widely used in the literature. For ease of understanding, I suggest changing this to “the broad phenotypic spectrum of DADA2 which makes early diagnosis challenging”

Reply 9: I have replaced the word “protean” as advised. **The changes are marked in blue in the text.**

Changes in the text: see Page 2, line 35 to 36; Page 6, line 142.

Comment 10: Line 56 – Should be “in accordance with”.

Reply 10: I have revised it as advised, and **the change is marked in blue in the text.**

Changes in the text: Page 3, line 55.

Comment 11: Line 67 – Change “every day” to “per day”

Reply 11: I have changed “every day” to “per day,” as advised, and **the change is marked in blue in the text.**

Changes in the text: Page 3, line 67.

Comment 12: Line 68 –In “a mild enlargement” please remove the ‘a’ as not needed.

Reply 12: I have removed “a” as advised. [The change is marked in blue in the text.](#)

Changes in the text: Page 3, line 68.

Comment 13: Line 72 –Could you comment on whether the child was anaemic, erythroaenic or lymphopaenic? Did he have immunoglobulins measured at any point? If so, please include these.

Reply 13: I have added initial full blood count (FBC) results to the text and placed the results of multiple FBC and immunological tests in the Supplementary Tables. [The change is marked in blue in the text.](#)

Changes in the text: Page 3, line 72 to 74; Page 4, line 77.

Comment 14: Line 77 – You could mention Figure 1 here and say “with concomitant reduction in CRP and ESR”. Tocilizumab is spelt incorrectly on Figure 1 (missing an ‘o’). In fact I think you forgot to make reference to Figure 1 in the text!

Reply 14: I have mentioned Figure 1 and added “with concomitant reductions in CRP and ESR” in the text. I have corrected the misspelling of tocilizumab on Figure 1. [The changes are marked in blue in the text.](#)

Changes in the text: Page 4, line 85.

Comment 15: Line 80 – Change “His doctor attributed this to the adverse effects of tocilizumab” to “His doctor attributed this to and adverse drug reaction”. You do not need to say tocilizumab again as you mentioned it in the preceding sentence.

Reply 15: I have modified the sentence as advised. [The change is marked in blue in the text.](#)

Changes in the text: Page 4, line 88 to 89.

Comment 16: Line 82 Hypertension. Was his hypertension symptomatic? Was a renal doppler ultrasound ever performed? Was his renal function normal? Was there any proteinuria or hypoalbuminaemia? Please state values if normal (can put in supplementary information some further blood results e.g. ferritin, LDH etc).

Reply 16: His hypertension was asymptomatic. Renal Doppler ultrasound, renal function, serum biochemical assays, and urine routines were all normal. I have mentioned them in supplementary data as advised. [The change is marked in blue in the text.](#)

Changes in the text: Page 4, line 87, 90, 91 and 92.

Comment 17: Line 89 – Did he ever have and MRA or MRI head. Please comment on this e.g. any evidence of stroke in this patient?

Reply 17: The patient had not experienced any neurological symptoms, including stroke; therefore, no head MRI or MRA were performed. I have mentioned this as advised. [The change is marked in blue in the text.](#)

Changes in the text: Page 4, line 99 to 100; Page 5, line 101.

Comment 18: Line 99 – Re-refer to Figure 1 please e.g. (Figure 1) at the end of the sentence.

Reply 18: I have revised it as advised. [The change is marked in blue in the text.](#)

Changes in the text: Page 5, line 111.

Comment 19: Line 104 – Which brand of anti-TNF was it? Adalimumab? Ertanercept? Please specify which other medications were continued to make it clear in the text (even though mentioned in Figure 2)

Reply 19: I have mentioned which anti-TNF was used, i.e., adalimumab, as required. I have specified the medications that were continued. [The changes are marked in blue in the text.](#)

Changes in the text: Page 5, line 116.

Comment 20: Line 109 – china should be China (capital letter) and change “in china and firstly described the deficiency of ADA2” to “in China who first described DADA2 in 2014”.

Reply 20: I have changed “china” to “China” and have modified the sentence as advised. [The changes are marked in blue in the text.](#)

Changes in the text: Page 5, line 121.

Comment 21: Line 112 – Did the child have any siblings? You say blood was not collected from the mother but make reference to mutation in the mother’s genetics in Figure 3B. Are you inferring that from the proband as he is a heterozygote or did you eventually get blood from the mother? However, I see that the you do not have ADA2 enzyme activity for the mother. Please clarify in the text and Figure.

Reply 21: The patient is an only child. His parents are divorced and his mother lives in another city. When we initially suggested whole-exome sequencing, his mother agreed, and her blood sample was obtained. However, she refused to provide blood for ADA2 enzyme activity testing. I have clarified briefly in the text and the Figure as required. [The changes are marked in blue.](#)

Changes in the text: Page 3, line 71; Page 5, line 123 to 125; Page 13, line 311 to 312.

Comment 22: Line 114 – omit the word ‘became’

Reply 22: I have removed the word “became.”

Changes in the text: Page 6, line 126.

Comment 23: Line 139 – Please mention negative clinical features in the main case report when you are describing the clinical features. Please put a supplementary table of results to support this e.g. full blood count results, B and T cell subsets (if you have them), immunoglobulins and other blood results if you have them. If you don’t have extensive immunology results please state the immunisation status of the child and

whether he was free from infections prior to first presentation.

Reply 23: I have included some negative symptoms associated with the diagnosis in the case description section. [The change is marked in blue in the text.](#) The results of full blood count, lymphocyte subsets, immunoglobulins, ANAs, and blood biochemistry are also placed in supplementary tables.

Changes in the text: Page 3, line 66; Page 3, line 70; Page 4, line 78, 91 and 92.

Comment 24: Line 143 – Remove ‘s’ from presentations (presentation)

Reply 24: I have changed “presentations” to “presentation”; [the change is marked in blue in the text.](#)

Changes in the text: Page 7, line 157.

Comment 25: Line 159 – yes but this is variable, along a spectrum. There are some patients with vasculitis with undetectable ADA2 activity.

Reply 25: I have modified the description as advised, and [the change is marked in blue in the text.](#)

Changes in the text: Page 7, line 173 to 174.

Comment 26: Line 159-161 – Remove this sentence. It is clear that there is variable penetrance with this disease, although the exact mechanisms are unclear.???

Reply 26: I have removed this sentence as advised.

Changes in the text: Page 7, line 174.

Comment 27: Line 166 – Change “Many immunosuppressants...” put In DADA2 patients many immunosuppressive treatments are often used with poor or unsustained clinical responsiveness”

Reply 27: I have modified the sentence as required and [the change is marked in blue in the text.](#)

Changes in the text: Page 8, line 180 to 181.

Comment 28: Line 167 – Change “Tocilizumab was successful in a DADA2 patient with a Castleman-like presentation” to “Tocilizumab has been used successfully in a patient with a Castleman Disease like presentation of DADA2”

Reply 28: I have modified the sentence as advised, and [the change is marked in blue in the text.](#)

Changes in the text: Page 8, line 182 to 183.

Comment 29: Line 168 – Anti-TNF therapy ‘is’ the mainstay....and ‘is’ highly efficacious.... (rather than was). If you are using the term anti-TNF therapy, please use this all the way through the text as earlier you use TNF alpha inhibitor. Be consistent.

Reply 29: I have changed the word “was” to “is” as advised. I have changed “anti-TNF therapy” to “**TNF- α** inhibitor” throughout the text. [The changes are marked in blue in the text.](#)

Changes in the text: Page 8, line 185.

Comment 30: Line 170 – Prevent strokes. Please reference papers here e.g. Cooray et al. and the Umbrello one.

Reply 30: I cited the two references suggested, and [highlighted them in blue](#).

Changes in the text: Page 8, line 187.

Comment 31: Line 173. – Did you check for anti-drug antibodies in this patient? Did you switch to other anti-TNF drugs e.g. etanercept? This is normally the practise before going to thalidomide or BMT. Was the patient/parent adherent to treatment? Can you expand a bit on the evidence for thalidomide and the clinical decision making for this?

Reply 31: We have not checked for anti-drug antibodies because we were unable to perform this test. We did not switch to “etanercept” because it is expensive due to frequent dosing (twice a week). The patient’s father had agreed to the treatment, but his financial situation was not very good to support the long-term treatment. We hoped to find a cheaper drug. Thalidomide has anti-TNF alpha properties (Thalidomide selectively inhibits tumor necrosis factor alpha production by stimulated human monocytes. *J Exp Med* 1991; 173:699–703.) and provided complete remission in a subset of DADA2 patients in an Italian cohort study (ADA2 deficiency (DADA2) as an unrecognised cause of early onset polyarteritis nodosa and stroke: a multicentre national study. *Ann Rheum Dis.* 2017;76(10):1648–56.). The results of the cohort study showed that thalidomide is an effective and less expensive alternative therapeutic strategy; therefore, we adopted combination therapy with thalidomide. I have included relevant content in the article and cited relevant literatures as advised.

[The changes are marked in blue in the text.](#)

Changes in the text: Page 8, line 187 to 190.

Comment 32: Line 177 – Mention gene therapy or recombinant pegylated ADA2 may be an option in the future (being used in cancer Targeting Adenosine with Adenosine Deaminase 2 to Inhibit Growth of Solid Tumors - PubMed (nih.gov))

Reply 32: I have mentioned gene therapy and recombinant pegylated ADA2, and cited relevant references. [The changes are marked in blue in the text.](#)

Changes in the text: Page 8, line 194 to 195; Page 8, line 198 to 199.

Comment 33: Line 188 – Change “of the diseases” to “of disease”

Reply 33: I have changed “of the disease” to “of disease,” as advised, and [marked it in blue in the text.](#)

Changes in the text: Page 9, line 210.

Second external peer review

Replies to comments from reviewer C

Comment: Line 28: systemic onset juvenile idiopathic arthritis (soJIA) *use this abbreviation

Reply: As required, I use this abbreviation soJIA throughout the text. The changes are marked **in red** in the text.

Changes in the text: Line 28, 54, 79, 82, 95, 111, 134 and 135.

Comment: Line 46: caused by autosomal recessive bi-allelic loss-of-function mutations in ADA2

Reply: I have modified the sentence as advised (removed the word “an”). The change is marked **in red** in the text.

Change in the text: Line 46.

Comment: Line 70: or physical signs

Reply: I have changed “and” to “or”, and the change is marked **in red** in the text.

Change in the text: Line 70.

Comment: Line 76: routine biochemistry and immunology tests were normal

Reply: I have modified the sentence as advised. The change is marked **in red** in the text.

Change in the text: Line 76.

Comment: Line 80: soJIA

Reply: I have changed “sJIA” to “soJIA”, and the change is marked **in red** in the text.

Change in the text: Line 79.

Comment: Line 88: this was attributed to a severe drug reaction (remove his doctor)

Reply: I have modified the sentence as advised. The changes are marked **in red** in the text.

Changes in the text: Line 87 to 88.

Comment: Line 91: Renal doppler ultrasound, routine urine testing, and serum biochemical assays were all normal

Reply: I have modified the sentence as advised. The changes are marked **in red** in the text.

Changes in the text: Line 90.

Comment: Line 95: tocilizumab and resolved following the treatment

Reply: I have modified the sentence as advised. The change is marked **in red** in the text.

Change in the text: Line 94.

Comment: Line 96 and Line 112: soJIA

Reply: I have changed “sJIA” to “soJIA”, and the changes are marked **in red** in the text.

Change in the text: Line 95 and 111.

Comment: Lines 123-125:). A blood sample was obtained from the mother for gene sequence analysis but a second sample could not be obtained for ADA2 enzyme activity testing.

Reply: I have modified the sentence as advised. The changes are marked **in red** in the text.

Changes in the text: Line 122 to 124.

Comment: Line 135-136: soJIA

Reply: I have changed “sJIA” to “soJIA”, and the changes are marked **in red** in the text.

Change in the text: Line 134 to 135.

Comment: Line 174: undetectable

Reply: I have changed “undetected” to “undetectable”, and the change is marked **in red** in the text.

Change in the text: Line 173.

Comment: Line 183 of DADA2 (15), however, (you have started the sentence with although so must continue the sentence rather than using a full stop)

Reply: I have modified the sentence as advised. The changes are marked **in red** in the text.

Change in the text: Line 182.

Comment: Line 184: *Can mention financial constraints here in your particular healthcare system as this is important for consideration of less expensive alternatives

Reply: I have mentioned the patient’s health insurance and his family’s financial situation as required. The change is marked **in red** in the text.

Change in the text: Line 186 to 188.