

MATTERS ARISING

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Responding to comments on “The possible pathogenesis of macular caldera in patients with North Carolina macular dystrophy.”

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Thanks to Dr. Kent W. Small’s supplementary description of NCMD subtypes, here we only give a general description to lead to the content we hope to discuss next.

Dr. Small points out an error in our article, that is, “chromosome 16q16 needs to be corrected to 6q16”, which is important for readers to know. We also agree with Dr. Small’s opinions on and additions to the references. Since the main research perspective of this article was clinical and imaging findings, it was inevitable that there would be omissions about the genetics. We thank Dr. Small for his supplemental information that made our article more complete [1–15].

In the studies he provides, we do not find a description of a Chinese or Asian family with NCMD [14]. Therefore, we recommend some supplementary annotated information to give the reader any available information along those lines.

In our study, whole-genome sequencing (WGS) was not performed. Based on existing clinical features and imaging and genetic evidence, we consider the diagnosis of MCDR1 in this family to be reliable. Because of economic and technological constraints, most patients cannot undergo WGS or related professional genetic analyses in clinical settings. Therefore, it is still worthwhile to research and discuss economical but reliable clinical diagnostic criteria for NCMD. Given the current

state of the art, it is true that WGS can provide patients with more valuable information, so we recommend that patients with applicable conditions undergo WGS whenever possible. This is also the focus of our next efforts [15, 16]. Regarding gene therapy, this article merely presents a potential concept. As Dr. Small has noted, the specific technical aspects still require further investigation.

We thank Dr. Small for providing additional references on PRDM13 and the diagnosis and misdiagnosis of NCMD. Additionally, we appreciate the notification to replace “Kent et al.” with “Small et al.” in some references [9, 10, 13, 17].

In the part on general clinical manifestations, the description of some family members with poor vision included the patient’s subjective feelings, and we also reported the patient’s specific visual acuity (VA). Through the descriptions in the article, it should not be difficult for readers to conclude that most NCMD patients have relatively good VA and can maintain their vision in the long term.

We agree with Dr. Small’s statement that macular abnormalities in NCMD are congenital macular hypoplasia/dysplasia, that is, a disease caused by abnormal embryonic development that exists at birth [12, 14, 15]. However, this term may not fully explain the specific pathogenic mechanisms underlying maculopathy in NCMD grade 3. Based on the imaging changes in this family, we speculate that during the macular development period of patients with grade 3 maculopathy, abnormalities in the retinal pigment epithelium (RPE) and choroid lead to neurosensory retinal degeneration. This process resembles atrophy; hence, the term ‘atrophy’ is employed to denote that process. Here, ‘atrophy’

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and ‘hypoplasia/dysplasia’ are not mutually exclusive but rather complementary in nature. As research advances, we anticipate the emergence of more precise terminology to delineate the specific pathogenic processes of maculopathy in this disease.

Finally, thanks to Dr. Small for his valuable comments on the usage of the term “caldera” in our article [8].

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ZZ and JX conceived and wrote this response.

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