Received: 14 April 2022 | Accepted: 15 April 2022

DOI: 10.1002/hep4.1984

CORRESPONDENCE

Letter to the editor: The clinically relevant *MTARC1* p.Ala165Thr variant impacts neither the fold nor active site architecture of the human mARC1 protein

To the editor,

We have read the recent publication by Hudert et al. in *Hepatology Communications* with great interest. In the article, a comprehensive study on the influence of a common variant of the mitochondrial amidoxime reducing component 1 (gene: MTARC1; protein: mARC1) on nonalcoholic fatty liver disease (NAFLD) in children is presented.[1]

Previously, genome-wide association studies have demonstrated that the p.Ala165Thr variant of *MTARC1* exerts a protective effect against NAFLD.[2,3] While Hudert et al. do confirm this protective effect in their study, they also show that the mutation does not influence hepatic *MTARC1* protein levels.

However, an alternative explanation for the phenotype associated with the variant is offered: using *in silico* tools, the authors predict loss of an alpha-helix and altered metal-ion binding ability of the protein. Furthermore, the variant is said to affect the overall stability of the protein.

These predictions are contradictory to previous findings from our group: None of the common variants of *MTARC1* have a significant influence on molybdenum saturations or *in vitro* enzymatic activity of recombinantly expressed proteins.[4]

More significantly still, we were recently able to determine the crystal structure of the variant at near-atomic resolution. The structure has the PDB accession code 7P41, and experimental details are also publicly available.[5] Briefly, while the electron density of the mutated residue is well-defined, no other alterations of the structure are observed: The alpha helix

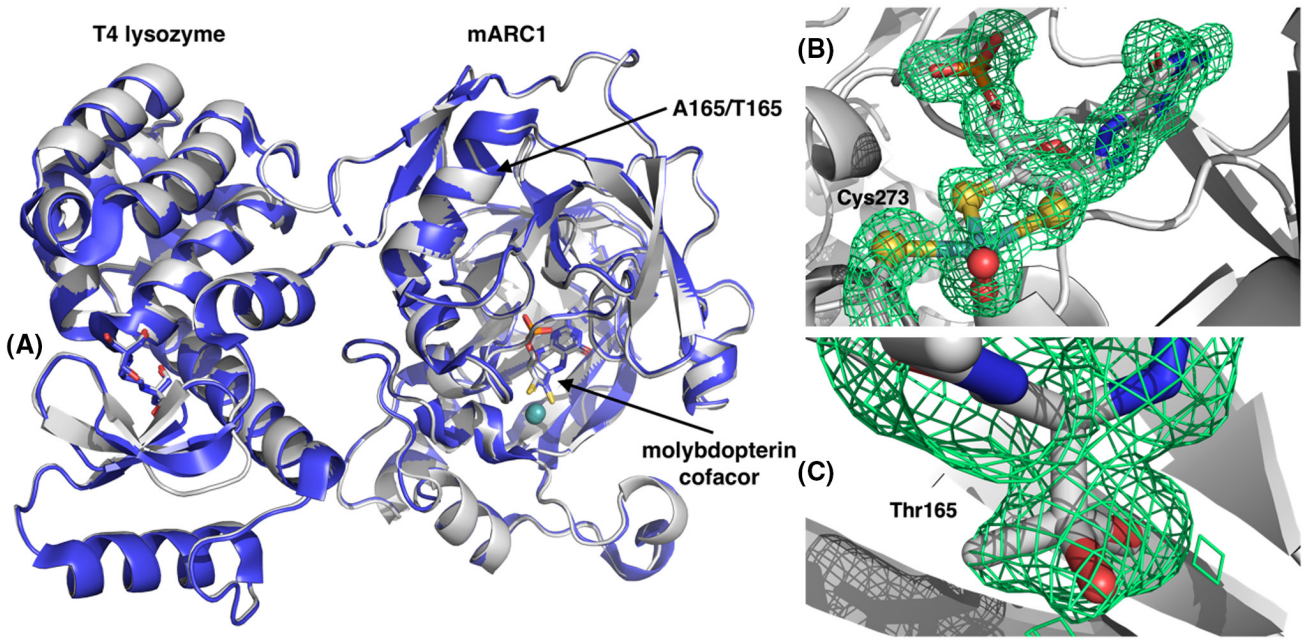

FIGURE 1 (A) Superimposed structures of both wild-type (blue) and variant (gray) mARC1 (mitochondrial amidoxime reducing component 1) as fusion proteins with T4 lysozyme. The fold of both proteins is identical. (B) Electron density surrounding the molybdenum site clearly shows an intact pentacoordinate molybdenum site. (C) Thr165 with electron density indicating two conformations of Thr165

predicted to be lost in the variant is fully intact, as is the molybdopterin cofactor and the molybdenum ion's coordination environment (Figure 1).

We therefore suggest that another, yet unknown mechanism is responsible for the phenotype of the *MTARC1* p.Ala165Thr variant. A loss of function due to incorrect folding or impaired molybdenum binding is likely to be too simple an explanation and is not supported by experimental evidence.

CONFLICT OF INTEREST

Nothing to report.

Michel A. Struwe[1,2]
Bernd Clement[2]
Axel Scheidig[1]

[1]*Zoologisches Institut/Strukturbiologie, Christian-Albrechts-Universität zu Kiel, Kiel, Germany*
[2]*Pharmazeutisches Institut, Christian-Albrechts-Universität zu Kiel, Kiel, Germany*

Correspondence
Axel Scheidig, Christian-Albrechts-Universität zu Kiel, Zoologisches Institut/Strukturbiologie, Kiel, Germany.
Email: axel.scheidig@strubio.uni-kiel.de

ORCID

Michel A. Struwe https://orcid.org/0000-0001-6931-1841
Bernd Clement https://orcid.org/0000-0003-1412-6117
Axel Scheidig https://orcid.org/0000-0002-2382-8818

REFERENCES

1. Hudert CA, Adams LA, Alisi A, Anstee QM, Crudele A, Draijer LG, et al.; EU-PNAFLD Investigators. Variants in mitochondrial amidoxime reducing component 1 and hydroxysteroid 17-beta dehydrogenase 13 reduce severity of nonalcoholic fatty liver disease in children and suppress fibrotic pathways through distinct mechanisms. Hepatol Commun. 2022 Apr 11. https://doi.org/10.1002/hep4.1955. [Epub ahead of print]
2. Emdin CA, Haas ME, Khera AV, Aragam K, Chaffin M, Klarin D, et al. A missense variant in mitochondrial amidoxime reducing component 1 gene and protection against liver disease. PLoS Genet. 2020;16:e1008629.
3. Schneider CV, Schneider KM, Conlon DM, Park J, Vujkovic M, Zandvakili I, et al. A genome-first approach to mortality and metabolic phenotypes in MTARC1 p.Ala165Thr (rs2642438) heterozygotes and homozygotes. Med (N Y). 2021;2:851–63. e853.
4. Ott G, Reichmann D, Boerger C, Cascorbi I, Bittner F, Mendel RR, et al. Functional characterization of protein variants encoded by nonsynonymous single nucleotide polymorphisms in MARC1 and MARC2 in healthy Caucasians. Drug Metab Dispos. 2014;42:718–25.
5. Struwe MA, Clement B, Scheidig AJ. The clinically relevant MTARC1 p.Ala165Thr variant impacts neither the fold nor active site architecture of the human mARC1 protein. bioRxiv. 2022. 2022.2003.2026.485076.