Human Genomics

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Response to Letter to the Editor

Hiba Alblooshi[1] and Najla Aljaberi[2*]

To the editor

We thank Drs. Yang and Wang for their thoughtful comments and interest in our recent publication, "A novel LACC1 variant c.658G > A (p.Asp220Asn) in familial juvenile idiopathic arthritis: identification and functional analysis" [1]. We appreciate their insightful discussion highlighting areas for further mechanistic exploration and future directions.

We address their main points as follows

1. Functional characterization and possible dominant-negative effects

We agree that differentiating between a pure loss-of-function (LOF) and a dominant-negative (DN) mechanism represents an important avenue of investigation particularly given the lack of full understanding of the function of LACC1 protein. Although other *LACC1* variants were associated with significant reduction of protein expression [2], our variant exhibited variable expression indicating other possible explanations for disease development. While assessing pro-inflammatory cytokine production would provide valuable insights,findings from the literature are conflicted about the effect of *LACC1* mutations on pro-inflammatory cytokines secretion [2–5]. Investigating additional pathways linked to LACC1 function is warranted to better understand the diverse mechanisms contributing to disease.

2. Phenotypic variability among affected siblings

We appreciate the authors' comments on clinical heterogeneity. We agree that factors such as epigenetic modifications, environmental exposures, and microbiome composition may contribute to the variable disease manifestations observed within the same family. Our ongoing efforts include transcriptomic profiling of patient-derived immune cells may shed light on molecular modifiers that influence disease severity and phenotype.

3. Structural and metabolic implications of the variant

We agree that molecular dynamics (MD) is an appropriate approach to probe the mechanistic impact of this mutation. In follow-up work, we will perform simulations of the wild-type protein and the mutant. This analysis will assess effects of mutation on local stability and helicity, particularly given that the substitution occurs at the N-terminus of an α-helix where interacting residues are highly conserved; accordingly, we hypothesize that the mutation perturbs helix formation or capping. We note that subcellular localization cannot be inferred from MD in a straightforward way. We are aiming to establish collaborations to perform metabolic flux analyses in macrophages derived from affected individuals. These studies will expand upon our current findings and clarify the biochemicalconsequences of LACC1 deficiency.

In summary, we appreciate the authors' constructive feedback and the opportunity to discuss these important mechanistic aspects. Their comments align with our ongoing research trajectory aimed at integrating functional

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genomics, structural modeling, and systems-level analyses to advance understanding of LACC1-associated arthritis.

Sincerely,

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Author contributions
HA and NA wrote and reviewed the main manuscript.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

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References

1. Alblooshi H, Mustafa N, Khalam AA, Bharathan A, Mohammed E, Baydoun I, Allam M, Almansoori M, Fatima T, Aljaberi N. A novel LACC1 variant c.658G > A (p. Asp220Asn) in Familial juvenile arthritis: identification and functional analysis. Hum Genomics. 2025;19(1):85. https://doi.org/10.1186/s40246-025-00800-2.
2. Omarjee O, Mathieu AL, Quiniou G, Moreews M, Ainouze M, Frachette C, et al. LACC1 deficiency links juvenile arthritis with autophagy and metabolism in macrophages. J Exp Med. 2021;218(3):e20201006. https://doi.org/10.1084/jem.20201006.
3. Cader MZ, Boroviak K, Zhang Q, Assadi G, Kempster SL, Sewell GW, Saveljeva S, Ashcroft JW, Clare S, Mukhopadhyay S, Brown KP, Tschurtschenthaler M, Raine T, Doe B, Chilvers ER, Griffin JL, Kaneider NC, Floto RA, D'Amato M, Bradley A, Wakelam MJ, Dougan G, Kaser A. C13orf31 (FAMIN) is a central regulator of immunometabolic function. Nat Immunol. 2016;17(9):1046–56. https://doi.org/10.1038/ni.3532.
4. Lahiri A, Hedl M, Yan J, Abraham C. Human LACC1 increases innate receptor-induced responses and a LACC1 disease-risk variant modulates these outcomes. Nat Commun. 2017;8:15614. https://doi.org/10.1038/ncomms15614.
5. Skon-Hegg C, Zhang J, Wu X, Sagolla M, Ota N, Wuster A, et al. LACC1 regulates TNF and IL-17 in mouse models of arthritis and inflammation. J Immunol. 2019;202(1):183–93. https://doi.org/10.4049/jimmunol.1800636.

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