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Challenges in functional validation and mechanistic interpretation of a novel LACC1 variant in familial juvenile arthritis

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Abstract

In their recent publication, Alblooshi et al. report the identification and preliminary functional analysis of a novel LACC1 variant, p.Asp220Asn, associated with familial juvenile idiopathic arthritis. While their study provides a valuable genetic association, this letter offers a critical appraisal to contextualize the findings and propose essential future directions. We contend that the functional characterization, while indicative of a loss-of-function, is insufficient to distinguish it from a potential dominant-negative mechanism, a distinction with paramount implications for genetic counseling. Furthermore, the observed clinical heterogeneity within the family remains mechanistically unaddressed; we propose that integrating systems-level approaches, such as transcriptomics and microbiome analysis, is crucial to move beyond mere description. Finally, the structural and metabolic consequences of the variant are underexplored. Employing molecular dynamics simulations and profiling mitochondrial metabolism in patient-derived cells could definitively link this genetic lesion to LACC1's emerging role in immunometabolism. This critique aims to elevate the impact of the initial discovery by mapping a pathway for transforming a genetic association into a profound pathophysiological understanding.

To the Editor,

We read with considerable interest the recent study by Alblooshi et al. [1] describing the identification and functional characterization of a novel LACC1 variant (c.658G >A; p.Asp220Asn) in a familial case of juvenile idiopathic arthritis (JIA). The authors provide valuable genetic evidence linking this variant to disease and present in vitro data suggesting a loss-of-function mechanism. While this work contributes to the genetic landscape of JIA, we believe a more in-depth and mechanistic exploration of the findings could further clarify its implications and help guide future research.

One aspect that could be strengthened is the functional characterization of the p.Asp220Asn variant. The authors show reduced IL-1β and IL-6 production in transfected monocytes, concluding a loss-of-function (LOF) effect [2]. However, this assay alone may not distinguish between a pure LOF and a potential dominant-negative (DN) effect—a distinction with important implications for genetic counseling. Although the study assumes an autosomal recessive model based on familial segregation, the experimental approach, which used overexpression in a null background such as HEK293T, may not fully assess

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possible DN activity. To explore this further, it could be informative to examine cytokine production in primary immune cells from heterozygous carriers. If a DN effect were present, cells from these individuals might display an intermediate phenotype in cytokine production compared to wild-type and homozygous mutant cells under endogenous expression conditions. In addition, complementation assays in which the wild-type LACC1 allele is reintroduced into patient-derived primary cells (e.g., macrophages) could help determine whether the cellular phenotype is fully reversible, which would support a pure LOF mechanism [2, 3].

The observed clinical heterogeneity between the affected siblings—presenting with polyarticular and oligoarticular JIA—suggests the potential influence of disease modifiers not addressed in the current study. Describing this variability as due to "incomplete penetrance or modifying factors" offers a useful starting point; however, future work could explore more specific mechanistic hypotheses. For example, emerging evidence highlights the role of the gut–joint axis and epigenetic regulation in inflammatory arthritis [2, 4]. It is plausible that differences in gut microbiota or microbial metabolites between siblings could influence how LACC1 deficiency manifests clinically. A multi-omics approach—such as transcriptomic profiling of peripheral blood mononuclear cells and 16S rRNA sequencing of stool samples—might help identify molecular and microbial correlates of disease severity, moving from association toward mechanistic insight [3, 4].

Finally, the structural and functional consequences of the p.Asp220Asn substitution merit further investigation. While the authors reasonably propose protein destabilization, computational or experimental validation would strengthen this hypothesis. Molecular dynamics simulations could help model how replacing a charged aspartate with a neutral asparagine might perturb local protein structure—for instance, by affecting helix stability, interaction interfaces, or subcellular localization. Moreover, as LACC1 is increasingly understood as a metabolic enzyme, the p.Asp220Asn variant offers an opportunity to explore its role in immune cell metabolism [5]. Metabolic assays, such as Seahorse analyses to assess mitochondrial respiration and glycolysis in patient-derived cells, might reveal whether this variant impairs oxidative phosphorylation—linking the genetic finding to LACC1's emerging metabolic functions and enriching the pathophysiological narrative [4, 5].

In summary, the study by Alblooshi et al. provides an important identification of a novel LACC1 variant and opens several compelling questions for future research. A deeper understanding could be achieved by clarifying the genetic mechanism (LOF vs. DN), applying systems-level analyses to explain phenotypic variability, and integrating structural and metabolic assays to connect the variant to cellular pathophysiology. Such multi-faceted approaches may help translate genetic findings into actionable biological and clinical insight.

Sincerely,
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Author contributions

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Data availability

No data were generated or analysed for or in support of this paper.

Declarations

Competing interests

The authors declare no competing interests.

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