International Journal of Contemporary Pediatrics
Yadav A. Int J Contemp Pediatr. 2025 Jul;12(7):1277-1277
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291
DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20251893

Letter to the Editor

Co-occurrence of SLC7A7 mutation with a novel PACS2 variant in a child with lysinuric protein intolerance: expanding the clinical spectrum

Sir,

Lysinuric protein intolerance (LPI) is a rare, autosomal recessive metabolic disorder caused by mutations in the SLC7A7 gene, leading to defective transport of cationic amino acids. It typically presents with vomiting, failure to thrive, hepatosplenomegaly, protein intolerance, hyperammonaemia, pulmonary and renal systems.[1] Separately, heterozygous pathogenic variants in the PACS2 gene have been associated with early-onset developmental and epileptic encephalopathy (DEE66), marked by hypotonia, drug-resistant seizures, and global developmental delay, encephalopathy.[2] We report a 7-month-old male child whose initial presentation was persistent vomiting, developmental delay, poor weight gain, hypotonia, seizures, and acute encephalopathy. The patient required mechanical ventilation for a month and was subsequently discharged on syrup levetiracetam, benzoate citrulline, arginine and supportive care. But seizure wasn't controlled on a single antiepileptic and required escalation to additional antiepileptic medications. At 4 years of age, he again presented with various seizure types- generalised tonic-clonic, focal seizures, staring look, and drop attacks along with depressed consciousness requiring intensive care and managed as a refractory epilepsy treatment protocol. Investigations revealed elevated serum ammonia and a high anion gap metabolic acidosis. Tandem mass spectrometry showed low arginine and ornithine levels. Magnetic resonance imaging (MRI) brain demonstrated gyral and periventricular white matter atrophy. Clinical exome sequencing revealed a compound heterozygous pathogenic variants in SLC7A7: exon 4 (c-697_698 ins.., p.Tyr233phefs), exon 2 (c.285 del, p.Thr96 ProfsTer74), consistent with LPI. Interestingly, a new heterozygous missense variant of uncertain significance (VUS) was also identified in the PACS2 gene (c.989G>A; p.Ser330Asn), previously not reported with metabolic phenotypes. Given the severe hypotonia, refractory seizures, and encephalopathy- features not typically prominent in isolated LPI – the additional PACS2 variant may reflect a dual diagnosis or a modifying effect on the LPI phenotype. Two different de novo missense mutations, c.625G >A and c.631G >A, in the PACS2 gene are reported in the literature.[3] This novel variant (c.989G>A) may further expand the molecular spectrum of PACS2-related phenotypes. Written informed consent was obtained from the patient's guardian. To the best of our knowledge, this is the first report of co-occurring SLC7A7 and PACS2 gene variants with overlapping clinical features. This case highlights the evolving complexity in interpreting next-generation sequencing results and the need for genotype-phenotype correlation, especially in rare disorders.[4,5] Further functional studies and data sharing will help to elucidate the clinical relevance of such variant combinations.

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Cite this article as: Yadav A. Co-occurrence of SLC7A7 mutation with a novel PACS2 variant in a child with lysinuric protein intolerance: expanding the clinical spectrum. Int J Contemp Pediatr 2025;12:1277-1277.