

Blood Cancer Journal 15, 8 (2025)

## **CALRins5-mediated clonal hematopoiesis causes severe hemolytic anemia in a female *PGK1*Ser320Asn carrier**

- M. L. Morales
- H. Cano,
- B. de la Morena Barrio
- J. L. Vives Corrons
- E. J. Cuenca Zamora
- P. Garrido Rodríguez
- C. Bento
- J. Pereira
- J. Martínez Nieto
- T.H. Chen-Liang
- J. L. Fuster,
- S. Caracena,
- M. L. Lozano,
- R. Terueel Montoya
- J. Corral
- F. Ferrer Marín

Morales, M.L., Cano, H., de la Morena-Barrio, B. et al. CALRins5-mediated clonal hematopoiesis causes severe hemolytic anemia in a female *PGK1*Ser320Asn carrier. *Blood Cancer J.* 15, 8 (2025).

<https://doi.org/10.1038/s41408-025-01216-w>

**INTRODUCTION** Hereditary hemolytic anemias (HHA) are rare inherited red blood cell (RBC) disorders caused by genetic abnormalities (hemoglobinopathies/membranopathies/enzymopathies), characterized by anemia due to premature RBC destruction and intrinsic RBC defects. One of the rarer enzymopathies involves a deficiency in phosphoglycerate kinase 1 (PGK1), an X-linked gene critical for ATP production via glycolysis. PGK1 mutations causing deficiency (OMIM#300653) follow an X-linked recessive inheritance

pattern, affecting hemizygous males, while female carriers are generally asymptomatic or may have mild symptoms -consistent with mosaicism for PGK1 activity-[2]. Despite PGK1 is ubiquitously expressed, its deficiency mainly affects the blood, central nervous system (CNS), and skeletal muscle, resulting in chronic hemolysis - with or without anemia-, neurological disorders, or myopathies [1]. Likely explained by the causative PGK1 mutation, hemolytic anemias (HA) tends to cooccur with CNS defects, whereas myopathies are almost exclusively observed [3, 4]. To date, approximately 40 patients harboring 30 different mutations have been reported. This report presents the first case of severe HA in a female PGK1 mutation heterozygous carrier, which became apparent coinciding with the diagnosis of essential thrombocythemia (ET); and elucidates the mechanism by which a clonal disorder transforms a germline recessive disease into a tissue-specific dominant condition.