Conference Proceedings By
United Research Forum, London, UK

ORGANIZED BY
UNITED RESEARCH FORUM
(CONNECT WITH RESEARCH WORLD)

5th International Conference on
Pediatrics and Neonatal Care
July 21-22, 2026 | Vienna, Austria

**Elena Di Pierro**, Francesca Granata, Lorena Duca, Valeria Di Stefano, Giovanna Graziadei

*Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*

## Pediatric forms of porphyria: diagnosis and functional insights into gene variants

Porphyria comprise a heterogeneous group of rare genetic disorders caused by pathogenic variants in genes encoding enzymes involved in heme synthesis. Three forms: Erythropoietic ProtoPorphyria (EPP), Congenital Erythropoietic Porphyria (CEP) and δ-aminolevulinc acid dehydratase deficiency porphyria (ADP) typically present during childhood. Despite significant advances in genetic diagnostics, a substantial proportion of patients remain genetically unresolved, largely due to the high allelic heterogeneity of porphyria-associated genes. In many cases, next-generation sequencing (NGS) identifies rare variants located within promoter regions, non-canonical splice sites, deep intronic regions, or novel missense substitutions whose pathogenicity cannot be established without additional functional studies. These variants of uncertain significance (VUS) are not currently integrated into the porphyria diagnostic workflow, resulting in persistent diagnostic ambiguity, and adverse consequences for patient management, genetic counseling, and access to appropriate therapeutic interventions. By integrating advanced genomic approaches, in silico prediction tools, and functional studies in patient-derived samples and animal models, this work aimed to improve the detection and interpretation of novel genetic variants associated with porphyria. We identified four new deep intronic variants, located 650 - 2600bp from constitutive exons, as well as two adjacent nucleotide substitutions affecting the same amino acid residue, in seven unrelated patients with clinically overt disease. Functional analyses revealed that all deep intronic variants cause aberrant pseudoexon inclusion in the mature transcript, through the activation of cryptic splice sites, whereas coding variants can impair exon recognition by disrupting auxiliary splicing regulatory elements, such as exonic splicing enhancers (ESEs) and silencers (ESSs), resulting in exon skipping. Overall, this study provided definitive molecular diagnoses for affected patients and their families, substantially enhancing the diagnostic power and clinical value of genetic testing in porphyria.

**Keywords:** Porphyria, deep intronic genetic variants, variants of uncertain significance, functional characterization, mRNA Splicing

**Biography**

Medical biotechnologist with a PhD in Molecular Medicine and over 25 years of experience in rare hematological and metabolic disorders, particularly porphyria and hemoglobinopathies. I developed biochemical and molecular diagnostic assays for porphyria, resulting in three patents, and conducted research focused on factors underlying phenotypic variability, including the role of modifier genes and predisposing variants, leading to several peer-reviewed publications. I currently lead a research team and actively contribute to the International Porphyria Network (IPNET) and the Italian Group of Porphyria (GrIP). I also serve as scientific advisor and sub-investigator in clinical trials evaluating novel therapies for porphyria.



https://doi.org/10.51219/URForum.2026.Elena-Di-Pierro

ISBN: 978-1-917892-44-5