Developmental and epileptic encephalopathy 35 (DEE 35) is a severe neurological condition caused by biallelic variants in Inosine triphosphate pyrophosphatase (ITPA), encoding inosine triphosphate pyrophosphatase, an essential enzyme in purine metabolism.

Scala et al. delineated the genotypic and phenotypic spectrum of DEE 35, analyzing possible predictors for adverse clinical outcomes. They investigated a cohort of 28 new patients and reviewed previously described cases, providing a comprehensive characterization of 40 subjects. Exome sequencing was performed to identify underlying ITPA pathogenic variants. Brain MRI scans were systematically analyzed to delineate the neuroradiological spectrum. Survival curves according to the Kaplan-Meier method and Log-Rank test were used to investigate outcome predictors in different subgroups of patients. We identified 18 distinct ITPA pathogenic variants, including 14 novel variants, and 2 deletions. All subjects showed profound developmental delay, microcephaly, and refractory epilepsy followed by neurodevelopmental regression. Brain MRI revision revealed a recurrent pattern of delayed myelination and restricted diffusion of early myelinating structures. Congenital microcephaly and cardiac involvement were statistically significant novel clinical predictors of adverse outcomes. They refined the molecular, clinical, and neuroradiological characterization of ITPase deficiency, and identified new clinical predictors which may have a potentially important impact on diagnosis, counseling, and follow-up of affected individuals [1)].

1)

Scala M, Wortmann SB, Kaya N, Stellingwerff MD, Pistorio A, Glamuzina E, van Karnebeek CD, Skrypnyk C, Iwanicka-Pronicka K, Piekutowska-Abramczuk D, Ciara E, Tort F, Sheidley B, Poduri A, Jayakar P, Jayakar A, Upadia J, Walano N, Haack TB, Prokisch H, Aldhalaan H, Karimiani EG, Yildiz Y, Ceylan AC, Santiago-Sim T, Dameron A, Yang H, Toosi MB, Ashrafzadeh F, Akhondian J, Imannezhad S, Mirzadeh HS, Maqbool S, Farid A, Al-Muhaizea MA, Alshwameen MO, Aldowsari L, Alsagob M, Alyousef A, AlMass R, AlHargan A, Alwadei AH, AlRasheed MM, Colak D, Alqudairy H, Khan S, Lines MA, García Cazorla MÁ, Ribes A, Morava E, Bibi F, Haider S, Ferla MP, Taylor JC, Alsaif HS, Firdous A, Hashem M, Shashkin C, Koneev K, Kaiyrzhanov R, Efthymiou S, Genomics QS, Schmitt-Mechelke T, Ziegler A, Issa MY, Elbendary HM, Striano P, Alkuraya FS, Zaki MS, Gleeson JG, Barakat TS, Bierau J, van der Knaap MS, Maroofian R, Houlden H. Clinico-radiological features, molecular spectrum, and identification of prognostic factors in developmental and epileptic encephalopathy due to inosine triphosphate pyrophosphatase (ITPase) deficiency. Hum Mutat. 2022 Jan 6. doi: 10.1002/humu.24326. Epub ahead of print. PMID: 34989426.