Inosine triphosphate pyrophosphatase

Pyrophosphatase that hydrolyzes the non-canonical purine nucleotides inosine triphosphate (ITP), deoxyinosine triphosphate (dITP) as well as 2'-deoxy-N-6-hydroxylaminopurine triposphate (dHAPTP), and xanthosine 5'-triphosphate (XTP) to their respective monophosphate derivatives. The enzyme does not distinguish between the deoxy- and ribose forms. Probably excludes non-canonical purines from RNA and DNA precursor pools, thus preventing their incorporation into RNA and DNA and avoiding chromosomal lesions.

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].

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