Investigating the impact of the pathological human phosphoserine phosphatase N133S variant on serine synthesis

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L-serine plays crucial roles in various metabolic pathways, especially in the brain since it can be converted into D-serine and glycine, which are the main co-agonists of NMDA receptors. It is mainly synthesized starting from a glycolytic intermediate via the phosphorylated pathway (PP). This cytosolic pathway involves three enzymes, which have recently been proposed to form a transient assembly named "serinosome", previously published in: Rabattoni V et al. (2023) FEBS J 29015, 3877–3895. Phosphoserine phosphatase (PSP) catalyzes the last and irreversible step of the pathway, which is essential to push the overall pathway towards L-serine synthesis. Genetic alterations in PP enzymes are related to serine deficiency disorders that lead to severe neurological phenotypes.

A homozygous missense variant (c.398A>G, p.N133S) in the PSP encoding gene was identified in two siblings exhibiting a neurodevelopmental syndrome and myelopathy. Despite no significant alterations in protein conformation, dimeric oligomerization, enzymatic activity, and PP functionality, the recombinant N133S PSP shows reduced stability compared to wild-type PSP, a characteristic evident at the cellular level as well. Patients' fibroblasts present decreased levels of PP enzymes, along with partial nuclear and perinuclear localization of the PSP variant and increased perinuclear aggregates formation. These findings suggest that these alterations contribute to the formation of a dysfunctional serinosome, leading to reduced levels of L-serine, glycine, and D-serine, observed both in fibroblasts and serum of patients, which may explain their neurological traits.

This study on patients presenting the N133S PSP substitution contributes to our understanding of the molecular mechanisms underlying alterations in serine levels. It also offers valuable insights into potential therapeutic strategies aimed at restoring the balance and mitigating the associated neurological manifestations.