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Entitled

ELUCIDATING THE IMPACT OF AMINO ACID SUBSTITUTIONS IN LYSOSOMAL STORAGE DISORDERS: INSIGHTS ON INFANTILE GM1-GANGLIOSIDOSIS AND SCHINDLER DISEASE

by

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Abstract

Monogenic disorders, inherited conditions arising from single gene defects, include more than 8,000 different entities with a worldwide prevalence of 10/1000 individuals. Disease causing missense variants are very common in monogenic disorders and may lead to various consequences at the protein and cellular levels. Therefore, a monogenic disease may show variable onset, symptoms, and severity based on the type and position of the mutation. Lysosomal storage disorders (LSDs) are a group of more than 60 monogenic metabolic disorders that are usually caused by deficiencies in specific lysosomal enzymes due to genetic defects in their coding genes. Of all reported LSDs' disease-causing mutations, the missense type is the most common covering more than two thirds of the identified variants. In this study, two clinical cases of two LSDs associated with different missense variants are presented. GM1-gangliosidosis is a severe neurodegenerative LSD caused by genetic defects in the GLB1 gene encoding β-Galactosidase (β-Gal) enzyme resulting in loss of residual enzymatic activity and the subsequent accumulation of its corresponding substrates in affected cells and tissues. Out of 222 GM1-gangliosidosis causing variants, of which more than 151 are the missense type. An Emirati child was admitted to the genetics clinic presented with an infantile form of GM1-gangliosidosis where whole genome sequencing analysis revealed the presence of a previously reported c.451G>T (p.D151Y) missense variant in the GLB1. The loss of function effect of the underlying variant was a result of β-Gal quantitative loss in lysosomes of patient's fibroblast cells due to its retention in the ER. Partial correction of the trafficking defect of p.D151Y β-Gal by glycerol and reduced temperature was an indication of its capacity to be rescued making it a potential candidate for enzyme enhancement therapy using pharmaceutical chaperones (PC). Indeed, the butyl derivative of Deoxygalactonojirimycin (DGJ) was able to partially promote the mutated β-Gal processing to lysosomes and significantly enhance its residual activity in patient's cells. On the other hand, Schindler disease is an autosomal recessive LSD caused by deficient alpha-N-acetylgalactosaminidase (α-NAGA) residual enzymatic activity. Out of twelve reported cases worldwide, six of which are carriers of missense variants with extreme variations in the clinical phenotype. A five-year-old Emirati child presented with severe neurological manifestations was confirmed to be a Schindler disease case based on the marked loss of enzymatic activity. Although his sister showed similar degree of enzymatic loss, she did not present clinical symptoms. Different molecular analyses revealed that the underlying amino acid substitution did not interfere with the enzyme processing and trafficking to lysosomes but negatively affected the enzyme active site pocket structural configurations that restricted its substrate binding. Overall, understanding the nature and the consequences of the causative genetic defects will improve the genotype/phenotype correlations and open new opportunities for therapeutic interventions.

Keywords: Lysosomal storage disorders, Missense variants, GM1 gangliosidosis, Schindler disease, Misfolded proteins, Pharmaceutical chaperones.