Molecular Case Studies of GALC Mutations Causing Krabbe Disease

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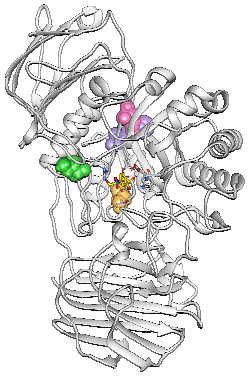
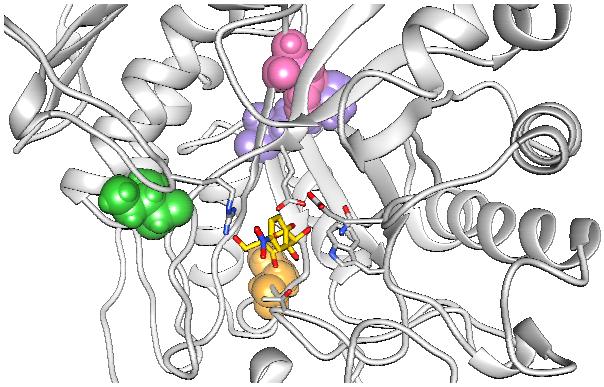
Globoid cell leukodystrophy, also known as Krabbe disease, [1] is a rare lysosomal disorder affecting the white matter of the central and peripheral nervous system. It is characterized by neurodegeneration and the most common form being infantile Krabbe cases, thus is usually diagnosed within the first year of life and with high morbidity and mortality. This autosomal recessive disease is caused by mutations in the GALC gene, which encodes the lysosomal enzyme galactocerebrosidase. [2] This study focuses on examining the structural effects of galactocerebrosidase variants found as mutations in the GALC gene of patients with Krabbe disease.





To investigate the effects of these mutations on protein structure, a structural model of human galactocerebrosidase was build. This model served as the basis for a series of all-atom molecular dynamics (MD) simulations to analyze the structural stability of the wild type and the mutated enzyme variants. Since galactocerebrosidase is subcellularly localized in the lysosome (pH 4.5-5.5), MD simulations were performed with protonation states corresponding to pH 4.5.

Differences in protein flexibility and intramolecular interactions between the wild type and the mutated enzymes were observed. Similarly, we detected effects of the mutations on the size of the substrate binding pocket, although the mutation site itself is not part of the active site/binding site of the enzyme.

Overall, our MD simulations shed light on how these mutations affect the structure of human galactocerebrosidase in the lysosome and they offer possible explanations as to why these mutations have an effect on enzyme function.

[1] Krabbe K: A new familial, infantile form of diffuse brain sclerosis. Brain,**1916**, *39*, 74–114.
[2] Suzuki K, Suzuki Y: Globoid Cell Leucodystrophy (Krabbe's disease): Deficiency of Galactocerebroside β-Galactosidase. Proc Natl AcadSci U S A **1970**, *66*, 302–309