Characterization of Iduronate-2-Sulfatase in Thai Patients with Hunter Syndrome: Biochemical and Molecular Pathogenesis

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ABSTRACT

Mucopolysaccharidosis Type II or Hunter syndrome is an inherited X-linked recessive disorder caused by the deficiency of a IDS gene coding iduronate-2-sulfatase (IDS) which results in the lysosomal accumulation of dermatan sulfate and heparan sulfate. As this accumulation continues, it interferes with certain cells and organs in the body and leads to a number of serious symptoms. Although this disease is rare, the number of newborns and children suffering from Hunter syndrome is significant. We have investigated enzyme changes and characterized IDS mutants in Thailand. Here, we identified 27 different mutants in 11 new mutations and 23 previously known protein variants. Ten patients with Hunter syndrome were analyzed in this study. The wild type and mutant (P.R101C, P.D148V, P.G224A, P.Y348X, P.R468P, and P.R468Q) were expressed in COS-7 cells to study enzyme activity and protein processing. Anti-human heparan sulfate revealed two precursor forms (76 kDa) and a mature form (55 kDa), whereas all mutants revealed only one precursor form except P.Y348X which had a truncated form at 50 kDa. Moreover, all mutants were modeled into the predicted three dimensional models of IDS using human arylsulfatase as a template. Most of mutants except P.D148V and P.Y348X were located near the active site (Cys84). These results indicate that these severe mutants may, at least in part, alter the protein processing and consequently lead to a decrease or absence in IDS activity, causing Hunter disease. This work was supported by Chulabhorn Research Institute, Thailand.

Keywords: Hunter syndrome, iduronate-2-sulfatase, mutation, protein processing, 3D-structure

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