[MS5-03] Insights into the mutations that cause Mucopolysaccharidosis I (MPS I) based on the structure and mechanism of a-L-Iduronidase

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Mucopolysaccharidosis type I (MPSI) is one of approximately 70 genetic disorders collectively known as the lysosomal storage diseases (LSDs). The gene underlying MPS I disease encodes the enzyme α-L-iduronidase (IDUA), that removes single α-L- iduronic acid residues from the non-reducing ends of the glycosaminoglycans (GAGs) heparan sulfate and dermatan sulfate.

We have crystallized human IDUA produced in the seeds of an Arabidopsis thaliana cgl mutant. The tertiary structure of IDUA has been determined in two different crystal forms; it consists of three domains, a TIM barrel (the catalytic domain), a β-sandwich domain and a C-terminal fibronectin-like domain. Structures of IDUA complexed with several IdoA analogues provide insights into Michaelis and product complexes and reveal an unusual 2,5B conformation of IdoA in the glycosyl-enzyme intermediate. In this conformation the C-5 carboxylate is equatorially disposed and interacts with a pair of positively-charged residues, Lys264 and Arg363 within the active site pocket These observations shed new light on a catalytic pathway employing the nucleophilic Glu299 and the general acid/base Glu182 in a retaining double displacement reaction.

Most importantly, these IDUA structures have enabled us to correlate the effects of several of the genetic point mutations responsible for MPS I to the clinical phenotypes.