A stable GH31 α-glucosidase as a model system for the study of mutations leading to human glycogen storage disease type II

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GH31 glycosidases are widespread across organisms, but, remarkably, less than 1% have been biochemically characterized to date. Among them, human lysosomal acid α-glucosidase (GAA) is notable due to its link to Pompe disease, a rare lysosomal storage disorder caused by its deficiency1. This disease results in glycogen accumulation, severe cellular damage, motor impairment, and premature death. Structural and functional studies of GAA mutants are challenging due to their instability and lack of activity, hindering their expression and purification. Here, we explore MalA, a GH31 enzyme from the hyperthermophilic archaeon Saccharolobus solfataricus, isolated from the Pisciarelli geothermal pool, as a stable homolog of GAA. This work exemplifies the valorization of unique biodiversity, harnessing the properties of an extremophile enzyme for biomedical research. MalA is highly expressible, easy to purify, and structurally characterized2. The R400H mutant in MalA, corresponding to the pathogenic GAA R600H mutation, revealed a 1200-fold drop in specificity constant and a >8 °C reduction in thermal stability. We report on MalA as a robust model for studying GAA mutations and developing therapeutic chaperones3.

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3 Iacono R, Paragliola FMP, Strazzulli A, Moracci M. J Enzyme Inhib Med Chem. 2025 Dec;40(1):2468859. doi: 10.1080/14756366.2025.2468859