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ACA 2018 Abstract
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Molecular mechanisms of enzyme dysfunction in PGM1 deficiency, an inherited metabolic disease

Human phosphoglucomutase-1 (PGM1) is essential for maintaining glucose homeostasis, acting as the pivot between energy storage and utilization. PGM1 deficiency, a recently reported inherited metabolic disease, is caused by mutations in PGM1 and has hallmarks of a classical glycogen storage disease as well as a congenital disorder of glycosylation. To date, we have determined the high resolution structure of the wild-type enzyme and 11 missense variants associated with disease. Direct structural information on these variants has allowed us to uncover and classify molecular mechanisms of dysfunction beyond the originally proposed binary classification of 'folding' and 'catalytic' mutants. Furthermore, we have conducted detailed molecular dynamics simulations and developed computational analyses to probe specific dynamic features to provide further validation of proposed disease pathways. Together our work provides a framework for personalized biophysics pipelines, demonstrates that PGM1 is a model system for study of inherited metabolic diseases, and elucidates nuanced dynamics within a robust structural architecture conserved through evolution.