Personalized biophysics of human PGM1 deficiency

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Phosphoglucomutase-1 (PGM1) is a central enzyme in glucose homeostasis where it acts as the pivot point between glucose utilization and storage. Mutations in PGM1 have been recently reported as the cause of PGM1 deficiency, an inherited metabolic disorder with features of both a glycogen storage disease and a congenital disorder of glycosylation. The disease presents with highly variable clinical phenotypes, including: dilated cardiomyopathy, hepatopathy, hypoglycemia, exercise intolerance, delayed puberty, and congenital malformations such as cleft palate. To uncover the molecular mechanisms of enzyme dysfunction in PGM1 deficiency we have determined the crystal structures of the wild-type (WT) enzyme and eight patient-derived missense variants. The structural perturbations introduced in these variants fall on a spectrum of dysfunction that include effects on folding, catalysis, and dynamics. For example, two Gly->Arg variants show localized regions of induced structural disorder not found in the WT enzyme. In another case, two physicochemically disparate mutations at the same position cause the loss of a conserved salt bridge. The lost interaction releases an Arg into the active site creating adventitious interactions stabilizing the active form of the enzyme and impeding catalysis. Together these data provide new insights into PGM1 mechanism and its highly robust structural architecture. These structures contribute to the field of personalized biophysics, and may be useful for the development of genotype-specific therapies.