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Structures of Human α -Phosphomannomutase 1 Reveal the Basis of Glycoprotein Syndrome Type 1a. Nicholas R. Silvaggi¹, Debra Dunaway-Mariano², Karen N. Allen¹, ¹Boston Univ. School of Medicine, Boston MA 02118; ²Univ. of New Mexico, Albuquerque, NM 87131.

Carbohydrate-deficient glycoprotein syndrome type 1a, a congenital disease characterized by severe nervous system defects, is caused by mutations in α -phosphomannomutase (α PMM). α PMM (there are two isozymes, α PMM1 and 2) catalyzes the conversion of D-mannose 6-phosphate to α -D-mannose 1-phosphate (M1P), a critical substrate in glycoprotein synthesis. The structure of human α PMM1 (29.7kDa) was determined alone and bound to M1P. α PMM1 crystallized in space group $P4_32_12$ with unit-cell dimensions $a=51.7\text{\AA}$ and $c=216.0\text{\AA}$. Surprisingly, molecular replacement using the structure of α PMM2 failed, despite 65% identity between the isozymes. Ultimately, the structure was determined to 2.1 \AA resolution ($R_{\text{cryst}}=0.191$, $R_{\text{free}}=0.206$) using a three-wavelength SeMet MAD data set collected at NSLS beamline X12C. This structure was used to phase the 1.8 \AA structure of the α -PMM1:M1P complex ($R_{\text{cryst}}=0.205$, $R_{\text{free}}=0.241$). The α -PMM1:M1P structure represents a collision complex, the first encounter of enzyme and substrate, and not the Michaelis complex. The substrate binds first to a cap domain and then is swept into the active site upon cap closure. Mapping the mutations onto the structure allows them to be classified as affecting substrate binding and catalysis, dimerization, or protein stability, with the most severe mutations falling into the first class.