A biophysical approach to study an orphan disease: the case of CblC, a rare disorder of vitamin B12 intracellular metabolism.

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The cblC disease is an inborn disorder of the vitamin B12 (cobalamin, Cbl) metabolism. The affected children manifest devastating symptoms involving vision, growth, and learning. The illness is caused by mutations in the gene codifying for MMACHC, a protein that transports and transforms the different Cbl forms. Although the crystal structure of the wild-type (WT) protein is available, a systematic study on the effect of each specific mutation on the resulting protein is still lacking. Here we present data on the biophysical characterization of WT MMACHC, and two variants resulting from CblC pathological mutations. By using a biophysical approach including spectroscopy, Dynamic-Static Light and Small X-Ray Angle Scattering, and Molecular Dynamics, we investigated protein structure/stability and ability to bind and transform Cbl. Moreover, we evaluated whether drug-like molecules identified by computational methods, or non-specific stabilizers (osmolytes) could restore functionality in MMACHC mutants. Overall our results reveal how a biophysical approach can offer new insights in the study of CblC mutations' specific effect and help prospecting new routes for the CblC treatment.