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 and 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 pathological mutations found in CblC patients. By using a biophysical approach including spectroscopy, Light and Small X-Ray Angle Scattering, Molecular Dynamics, we investigated protein structure/stability and ability to bind and transform Cbl. Moreover, we evaluated whether 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.