INVESTIGATION ON MMACHC-R161Q PATHOLOGICAL MUTANT FROM cblC DISEASE, A RARE METABOLIC DISORDER OF VITAMIN B12 METABOLISM

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The cblC disease is a rare inborn disorder of the vitamin B12 (cobalamin, Cbl) metabolism characterized by combined methylmalonic aciduria and homocystinuria. The clinical consequences are devastating and, even when early treated with current therapies, the affected children manifest symptoms involving vision, growth, and learning[1]. The molecular genetic cause of the disease was found in the mutations of the gene coding for MMACHC, a 282 amino acid protein that transports and processes the various forms of Cbl[2]. Although the crystal structure of the wild-type protein is available[3,4], many molecular features of MMACHC physiopathology remain to be understood and a systematic study on the effect of each specific mutation on the resulting protein is still lacking. Here we present the biophysical characterization of wild type MMACHC and a variant, p.R161Q, resulting from the most common missense pathological mutation found in CblC patients. By using a biophysical approach, we investigated the stability of the two proteins and their ability to bind and transform the vitamin B12[5], and to assemble in a dimeric structure. Moreover, we evaluated whether drug-like molecules identified by computational methods, or non-specific stabilizers (osmolytes) could restore the functionality in MMACHC mutant. Overall, our results reveal how a biophysical approach based on the complementarity of computational and experimental methods can offer new insights in the study of the specific effects of the pathological cblC mutation and help prospecting new routes for the cblC treatment.

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