Studying a rare disease from a biophysical point of view: the example of cblC

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A rare disease is defined by the European Union as a condition affecting fewer than 5 people per 10,000. Despite their rarity, these diseases pose a significant societal challenge, as effective treatments are often lacking due to limited investments, leaving patients and caregivers struggling to find adequate support networks.

Our work focuses on cblC disease, 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 severe symptoms including neurocognitive and cardiovascular dysfunctions[1].

Here, by using biophysical methods including spectroscopy, microcalorimetry and molecular dynamics we investigated the differences in stability, binding properties and functionality between wild type MMACHC protein and the pathological variant p.R161Q[2,3], resulting from the most common missense mutation found in cblC patients.

Altogether, our findings demonstrated how the combined use of computational and experimental biophysical approaches deepen the knowledge of the molecular mechanisms underlying the cblC. Understanding the specific chemical-physical defects induced by a given mutation is the first step toward implementing a potential personalized therapeutic intervention.

Furthermore, since many rare diseases share common mechanistic features driving molecular pathogenic events, the biophysics-based methodological toolbox presented here could also be valuable for studying other rare diseases.

1. Carrillo-Carrasco et al., Journal of inherited metabolic disease (2012) 35, 91-102
2. Passantino et al. BBA Proteins and Proteomics Proteins and Proteomics (2022) 1870(2):140793
3. Vilasi on the behalf of Longo et al., Il Nuovo Cimento 47 C (2024) 318