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

Lisa Longo, Rita Carrotta, Maria Assunta Costa, Rosa Passantino, Maria Rosalia Mangione,
Maria Grazia Ortore, Adrian Velazquez Campoy, Marco Tutone, Vincenzo Martorana, Silvia Vilasi

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. 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.

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

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.

Researcher involved:

Rita Carrotta: Researcher at Istitute of Biophysics (IBF), National Research Council (CNR), internal collaborator

Maria Assunta Costa: Researcher at Istitute of Biophysics (IBF), National Research Council (CNR), internal collaborator

Rosa Passantino: Researcher at Istitute of Biophysics (IBF), National Research Council (CNR), internal collaborator

Maria Rosalia Mangione: Researcher at Istitute of Biophysics (IBF), National Research Council (CNR), internal collaborator

Maria Grazia Ortore: Professor at Marche Polytechnic University, Department of Life and Enviromental Sciences, external collaborator

Adrian Velazquez Campoy: Professor at University of Zaragoza and Group Leader at the Institute for Biocomputation and Physics of Complex Systems (BIFI), supervisor during the research stay abroad

Marco Tutone: Professor at University of Palermo, Department of Biological, Chemical and Pharmaceutical Sciences and Technologies, co-supervisor

Vincenzo Martorana: Researcher at Istitute of Biophysics (IBF), National Research Council (CNR), supervisor

Silvia Vilasi: Researcher at Istitute of Biophysics (IBF), National Research Council (CNR), co-supervisor