Functional Recovery of a GCDH Variant Associated to Severe Deflavinylation — Molecular Insights into Riboflavin Supplementation in GA-I Patients

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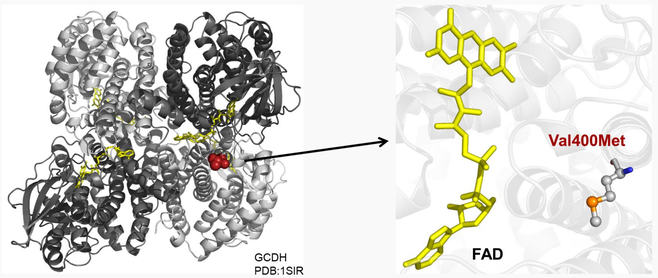
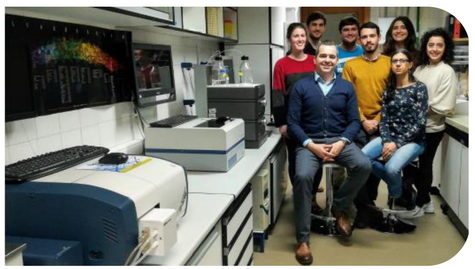
Outline of research

Glutaric Aciduria Type I (GA-I) is a neurometabolic disease caused by mutations in the *GCDH* gene, that encodes for the mitochondrial flavoprotein Glutaryl-CoA Dehydrogenase (**GCDH**). It has been established, for other metabolic disorders associated with defects in flavoproteins, that flavin (**FAD**) cellular availability can modulate the folding and activity of disease variants. Resorting to different biochemical and biophysical methods, we sought to elucidate on the molecular mechanism behind the therapeutic effects of riboflavin supplementation on GA-I patients. We chose as our model the **GCDH-p.Val400Met** variant, that has been previously described has having impaired flavin binding.

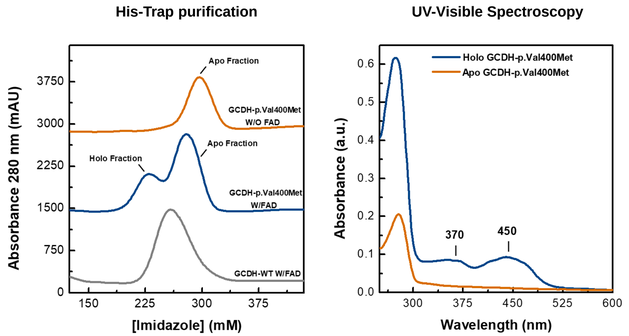


Localized near conserved region for FAD.

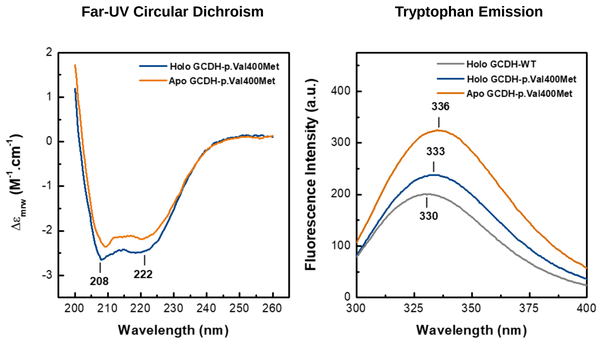


Results

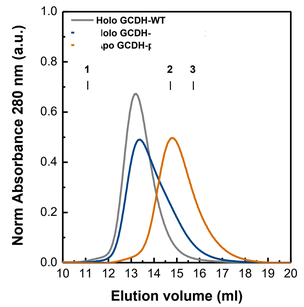
Purified human recombinant GCDH-p.Val400Met is depleted of FAD cofactor



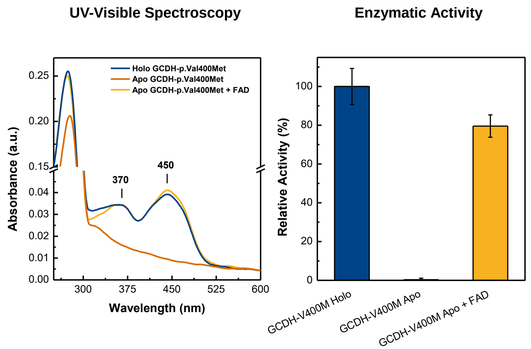
Apo GCDH-p.Val400Met Presents a Less Compact Conformation



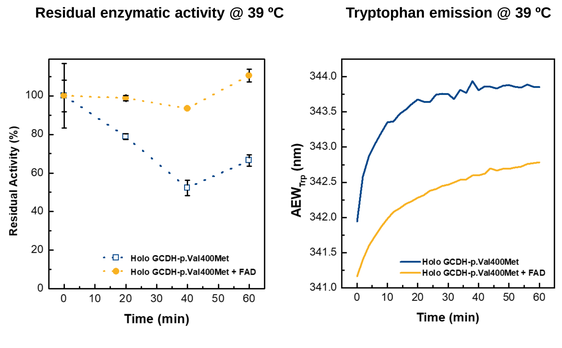
Deflavinylation Affects GCDH Quaternary Structure



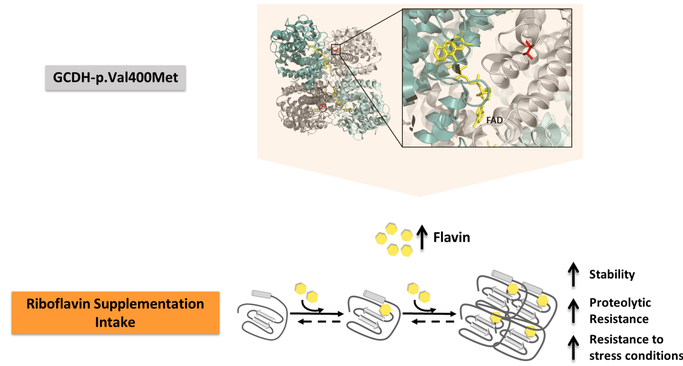
Flavin Supplementation Rescues Apo GCDH-p.Val400Met Enzymatic Activity



External FAD Preserves GCDH-p.Val400Met Enzymatic Activity during Thermal Stress



Conclusions



Our results suggest that riboflavin supplementation can be beneficial for patients with the Val400Met mutation, and also that other misfolded GCDH variants could benefit from this therapy.

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