

P004 Impaired iron binding and protein misfolding in clinical frataxin variants

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Deficiency in frataxin, an iron chaperone protein highly conserved throughout evolution, leads to the neurodegenerative disease Friedreich's Ataxia (FRDA). At the molecular level this disease is characterized by mitochondrial iron accumulation, deficiency in iron-sulphur proteins and increased oxidative stress.

Combining biophysical and biochemical methodologies, we have analysed *in vitro* the consequences of different disease related mutations (D122Y, G130V, I154F and W155R) on the folding/stability, dynamics and function of human frataxin. Our results show that, at 25°C, the mutations do not change significantly the protein fold or its flexibility. However, the mutants present a reduced thermodynamic stability, an increased propensity towards aggregation and their iron binding capacity is partially compromised. At 37°C, the mutants exhibit an increased structural flexibility which results in a higher proteolytic susceptibility.

Framing our results with the available *in vivo* data, suggests that the clinical effects in heterozygous patients may arise from a combination of reduced efficiency of protein folding and accelerated *in vivo* processing leading to levels of functional frataxin lower than normal. This hypothesis also suggests that FRDA could be linked to a process of protein misfolding due to specific destabilization of the protein involved.