Loss of stability and hydrophobicity of presenilin 1 mutations causing Alzheimer's Disease

Nearly 200 mutations in the gene coding for presenilin 1 (PSEN1) cause early-onset Alzheimer's Disease, yet the molecular mechanism remains obscure. As a meta-analysis, we compiled available clinical and biochemical data for PSEN1 variants and correlated these to chemical properties of the mutants. We found statistically significant relationships between relative Aβ42 levels and clinical age of onset. We then computed chemical properties of the mutants from a variety of computational chemistry tools. Relative Aβ42 levels correlated significantly (95% confidence or more from p-values of linear regression) with loss of hydrophobicity for four different regression analyses (squared correlation coefficient of linear regression $R^2$ of 0.41–0.51) and with increased polarity ($R^2 = 0.47, 0.59$) and loss of protein stability ($R^2 = 0.39, 0.63$) for two independent data sets. Age of onset of patients carrying PSEN1 variants correlated with increased polarity ($R^2 = 0.49, 0.40$) and loss of stability ($R^2 = 0.75, 0.44$) of the protein for both data sets. These relations suggest that mutants impair the membrane-associated structural integrity of presenilin by reducing hydrophobic membrane association and overall protein stability. This explains why the many mutations that spread out across the protein and far from the catalytic aspartates can cause disease. The identified molecular determinants of clinical age of symptom onset may be relevant to future presenilin-modulating therapies specifically directed towards increasing the structural integrity and packing of the protein.