

## A Proteomic Analysis with Suggested Applications in Amyloidotic Diseases

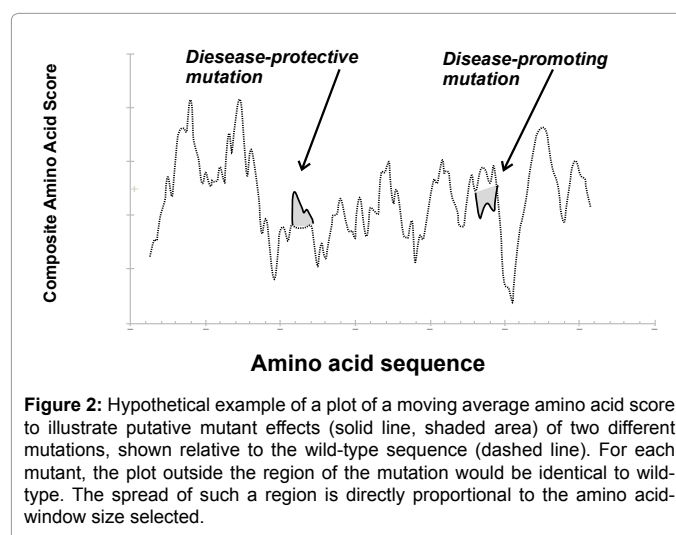
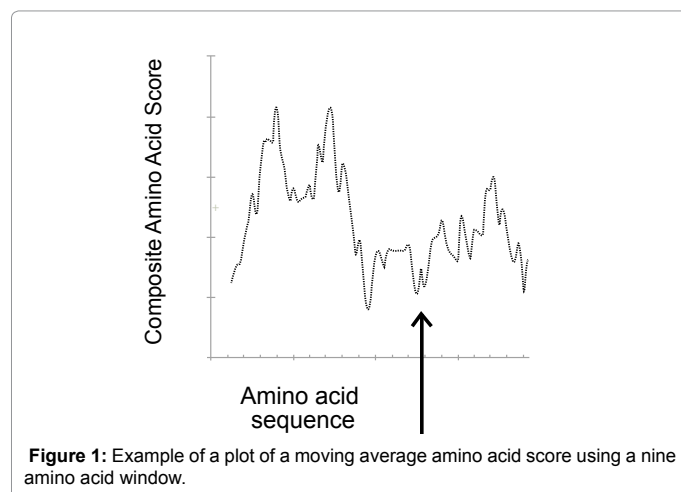
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Misfolded, aggregated proteins (agP) and peptides contribute to Alzheimer's, Parkinson's, and several other, lesser-known or less common, amyloidotic diseases. Table 1 lists some of these diseases and the associated agP or peptide; over 20 of these agP/peptides and related amyloidotic diseases are known. There is much interest in identifying the molecular and cellular toxicity mechanisms of these misfolded monomeric, oligomeric, and fibrillar forms. Mutant forms of an amyloidotic polypeptide may greatly increase its amyloidogenicity; but some mutant form may have greater stability and lower amyloidogenicity.

We have begun to analyze the primary structure of wild-type and mutant forms of amyloidogenic proteins such as transthyretin, apolipoprotein A1, and others in an attempt to correlate structural changes with disease severity. For example, amino acid biophysical properties such as hydrophobicity scores can be incorporated into a moving average 'window', e.g., nine amino acid units, and used to scan across the whole protein sequence. Figure 1 shows a plot of such a moving average as a structural representation of a protein.

The region around an amino acid mutation may differ between the wild-type and mutant, as shown in Figure 2, and the difference can be quantified using the areas under the curves (AUC). By using standards such as a mutation that is known to drastically change protein structure or is known to cause a severe form of disease, an optimization protocol can be developed to formulate the combination of amino acid biophysical properties which yield the greatest difference in AUC relative to the wild-type protein. Additional mathematical methods may be useful in analyzing the plots. Amino acid scores that may be integrated into an optimal score formula include size, charge, secondary structure frequencies, hydrophobicity, surface free energy, etc. And optimization may include factoring in the properties of the most frequent substitutions for a given amino acid. In conclusion, these analyses based on readily available amino acid sequences may be useful in terms of predicting some higher-level protein structural changes, and perhaps disease severity of some mutant forms.



Disease	Protein/peptide
Alzheimer's disease	Amyloid beta
Parkinson's disease	Alpha-synuclein
BSE and other encephalopathies	Prions
Familial visceral amyloidosis	Apolipoprotein A1
Familial amyloidotic polyneuropathy	Transthyretin
Type 2 diabetes (pancreatic deposition in some cases)	Amylin
Dialysis-related amyloidosis	Beta 2-microglobulin

**Table 1:** List of some amyloidotic diseases and the main polypeptides involved.

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