Neurodegenerative Proteinopathies

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Neurodegenerative Proteinopathies, also known as protein conformational diseases or amyloidosis, are a group of diseases associated with the deposition of misaggregated proteins in the nervous system.

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1. Introduction

Most of the common neurodegenerative disorders—Alzheimer's disease (AD), Parkinson's disease (PD), Creutzfeldt–Jacob disease (CJD), Dementia with Lewy bodies (DLB), Huntington disease (HD), and Amyloid Lateral Sclerosis (ALS)—are proteinopathies. Together, these diseases affect millions of lives around the world and have devastating economic implications. AD, the most frequently diagnosed among these listed diseases, affects almost one-tenth of the population above 65 years of age[1]. The number of people suffering from these diseases is increasing rapidly with an increase in life expectancy and it is predicted that by 2050, 135.46 million people will be living with various types of neurodegenerative dementias[2]. Despite the attention of the scientific community, these disorders are far from resolved. The patients can be treated to alleviate the symptoms, but the lack of a cure still means that such a diagnosis can seal their fate.

2. Amyloid

Although proteinopathies present similarities in their pathological mechanisms, the psychological and physiological symptoms of all these disorders vary and depend on the region of the brain affected. A summary of age at onset, primary sites of pathology, and common symptoms of major neurodegenerative proteinopathies is presented in Table 1. These variations, in turn, are dictated by the proteins that are involved in amyloid formation (Table 2).

Table 1. Age at onset, affected brain regions, and common symptoms of major neurodegenerative proteinopathies. Age at onset represents a range, rather than mean, due to multiple clinical variants of each of these disorders. * sporadic CJD.

Proteinopathy	Age at Onset (Years)	Primary Region	Common Symptoms
AD	40–65 (early and late-onset variants)	Hippocampus and entorhinal cortex.	Memory and language impairment and visuospatial deficits. [3][4]
PD	40–50	Substantia nigra (midbrain).	Rigidity, resting tremor and bradykinesia. [5]
sCJD *	44–70 (depends on subtype)	Cerebral cortex and cerebellum.	Cognitive impairment and myoclonus. [6]
DLB	50–80	Midbrain and neocortex.	Parkinsonian syndrome, autonomic and sleep fluctuations and hallucinations. [7]
HD	20–49	Caudate nucleus and putamen (basal ganglia).	Choreiform movements, emotional and behavioral alterations, bradykinesia. [8]
ALS	45–55	Motor neurons.	Focal muscle wasting, spasticity and flexor spasms. [8][9]

Table 2. A summary of the structure and variants of major amyloidogenic proteins associated with neurodegenerative proteinopathies.

Amyloids	Precursor Protein	Associated Diseases	Proteoforms or Other Variants
Aβ	**Amyloid beta A4 protein: Intrinsically disordered protein with 770 residues**	**AD, Cerebral amyloid angiopathy (CAA)[10][11].**	**26 differentially truncated and post translationally modified proteoforms [12]**
α-Synuclein	**Alpha Synuclein: Intrinsically disordered protein with 140 residues**	**PD and DLB [13]**	**11 differentially truncated and post translationally modified proteoforms [14]**
PrPSc	**Major prion protein: Intrinsically disordered protein with 253 amino acids**	**CJD, Fatal Familial Insomnia (FFI), Gerstmann-Straussler-Scheinker disease (GSS), Huntington disease-like type 1 (HDL1), Kuru and Spongiform encephalopathy [15]**	**2 Proteoforms based on Proteinase-K resistance Genetic variants (codon 129 polymorphism). [16]**
ASOD	**Superoxide dismutase: Intrinsically disordered protein with 154 amino acids**	**ALS—TDP-43 amyloids also involved. [17][18]**	**Genetic variants. No proteoforms reported yet. [19]**
ATau	**Microtubule-associated protein tau: Intrinsically disordered protein with 758 amino acids**	**Frontotemporal dementia (FTD), AD, Progressive Supranuclear Palsy (PSP), Corticobasal degeneration (CBD), Pick's disease, Argyrophilic grain disease, Dementia with Lewy bodies and Parkinsonism linked to chromosome 17. [20]**	**Six isoforms. Differentially post translationally modified proteoforms. [21]**
ATTR	**Transthyretin: Mostly β-sheet with 147 amino acids**	**Familial Amyloid polyneuropathy, Leptomeningeal amyloidosis. [22]**	**Differentially oxidized proteoforms. [23]**
AHtt	**Huntington: Intrinsically disordered protein with 3142 residues**	**Huntington disease. [24]**	**Differentially post translationally modified proteoforms. [25]**

In addition to similarities in the mechanism of propagation, prion-like proteins have also adapted another interesting aspect of PrPSc biology. PrPSc can give rise to several clinical variants of prion diseases. This heterogeneity has been attributed to the existence of distinct PrP strains. Strains are defined as conformers of a specific amyloidogenic protein, in this case PrPSc, that differ with respect to their transmission, brain-lesion profiles, incubation periods, and disease phenotypes along with certain biochemical characteristics like Post-translational modifications, sensitivity to proteinase-K, and electrophoretic mobility. The distinct conformational characteristics of each PrP strain are transmitted into the host where it propagates and causes distinct phenotypes[26]. Codon 129 polymorphism gives rise to at least three known strains of PrP in humans [27].

Strain theory is now applicable to most prion-like proteins (Figure 2)[28][29]. α-Synuclein, for example, has been known to be the culprit behind characteristically distinct pathologies, i.e., PD, DLB, and multiple system atrophy, while microtubule-associated protein tau is involved in multiple different tauopathies either as the primary cause or as a co-pathology [30][31]. In the case of Aβ, it has been known for several years that different proteoforms vary in their capability to form amyloids, seeding proficiencies, three-dimensional conformations, transport mechanisms and toxicities [32][33]. Each proteoform can adopt and propagate in multiple conformations [34]. These conformers do not only possess distinct biochemical signatures but also have different stabilities, distribution and morphology in the brain [35]. Moreover, accumulating evidence shows that many neurodegenerative proteinopathies can exist as rapidly progressive and other clinically distinct variants even though the underlying prion-like proteins and mechanisms are the same [36][37]. The capability of one protein to give rise to clinically distinct disorders and alter the progression of a disease has further complicated the characterization of neurodegenerative proteinopathies.

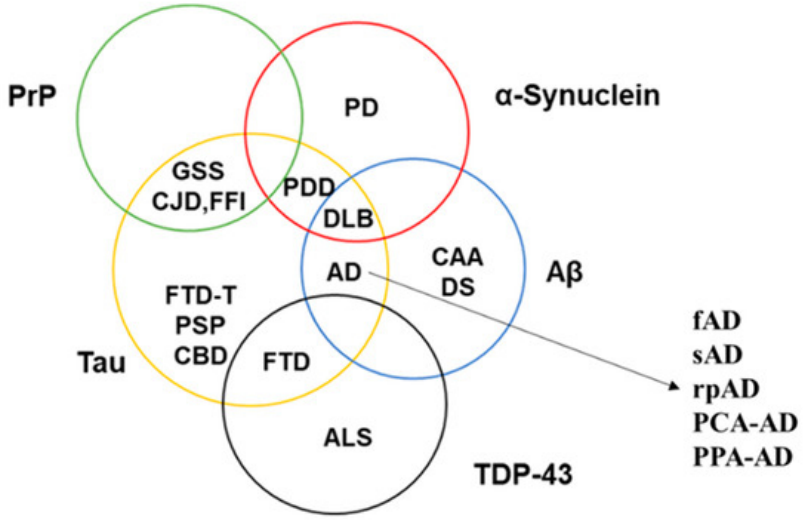

Figure 2. Involvement of known prion-like proteins in multiple neurodegenerative disorders. The figure depicts the overlapping pathological profile of PrP (green circle), α-Synuclein (red circle), Aβ (blue circle), Tau (yellow circle), and TDP-43 (black circle). Each of the stated disorders have further clinical variants (as shown in the case of AD), thereby complicating the role of prion-like proteins in bringing about the observed pathology. PDD—Parkinson's disease with dementia; DS—Down's syndrome; FTD-T—frontotemporal dementia with tau pathology; fAD—familial AD; sAD—sporadic AD; rpAD—rapidly-progressive AD; PCA-AD—posterior cortical atrophy–AD; PPA-AD—primary progressive aphasia with AD.

The study of prion-like proteins now encompasses the study of all variants/proteoforms rather than focusing on one parent entity. The existence of proteins as different functional variants is a known fact. These functional variants dictate the localization, uptake, recycling, and biological functions of a protein. In the case of prion-like proteins, the presence of distinct variants involved in neurodegenerative proteinopathies has been verified by several groups over the past two decades[12][14][38]. Although several different terms have been previously used in the literature to classify these variations, any prion-like protein can have:

- Genetic variants (based on mutations).
- Isoforms (based on differences in post-transcriptional modifications).
- Proteoforms (based on differences in post-translation processing and three-dimensional conformation).
- Strains (based on differences in infectivity and incubation periods).

With the acceptance of the notion that different isoforms, proteoforms, or strains of prion-like proteins may differ with respect to their molecular insult mechanisms and dictate the prognosis of associated pathology, the availability of high-resolution data about the sequence and structure has become the key in characterizing, diagnosing, and treating neurodegenerative proteinopathies [39][40][41][42][43][44]. It is therefore mandatory to establish tools that can provide insight into minor changes within the sequence, post-translational processing, and structure of a protein in its undigested form or native conformations.

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