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Decoding Protein Misfolding: Advances In Prion Disease Pathogenesis, Biomarker Discovery, And Therapeutic Development

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ABSTRACT

Prion diseases are among the class of transmissible neurodegenerative disorders that are universally fatal, and any disease mechanism involving misfolding of the native prion protein (PrP^C) into a pathogenic isoform (PrP^Sc). Examples of such disease states include Creutzfeldt-Jakob disease (CJD) and fatal familial insomnia (FFI), characterized by rapid clinical decline, frequent phenotypic variation, and an absence of disease-modifying therapies. Even though more and more people around the world are working on research about prion diseases, India still doesn't recognize them very well because of limited diagnostic tools, scattered epidemiologic evidence, and a lack of clinical awareness. There is no centralized or coordinated surveillance for cases of prion disease that can perform molecular diagnostics, which makes it hard to find and report these diseases quickly. This review summarizes the latest progress in prion biology and translational research, focusing on gene- and RNA-based therapies, AI-assisted diagnostic tools, and how findings from cross-disease proteinopathy studies relate to prion diseases. The review also discusses an integrative framework for India that utilizes genomic context, promotes amplifying growth through partnerships with institutions, and focuses on policy-level investment in the current advancements in precision medicine infrastructure.

Keywords: Science, Medical and Health Sciences, Neurology, Prion Diseases Protein, Misfolding & Neurodegeneration

1. INTRODUCTION

Transmissible spongiform encephalopathies (TSEs), or prion diseases, are a rare, always fatal group of neurodegenerative conditions caused by the misfolding and aggregation of a normal membrane protein called the cellular prion protein (PrP^C) into a pathogenic conformer (PrP^{Sc}).[1,2] Prions are different from other pathogenic infectious agents because they do not contain any nucleic acids and instead replicate by a mechanism whereby they induce substrate proteins to undergo structural conversion to their own pathogenic conformer to perpetuate a cycle of misfolding and neurotoxicity.[3] The mechanism of a unique self-replicating and protein-only infectious agent presents a range of challenges to experimental investigation and clinical interpretation.

Creutzfeldt–Jakob disease (CJD), which can present in sporadic, familial, iatrogenic, or variant forms,[4] and fatal familial insomnia (FFI), which is caused by specific mutations in the PRNP gene, are amongst the most scrutinized of the human prion diseases.[5] These diseases are characterized by quickly progressive cognitive dysfunction, ataxia, changes in behavior, and myoclonus, with death usually occurring within months after the onset of symptoms. The pathological features in prion diseases are essentially defined by the spongiform degeneration of grey matter, astroglial proliferation, and the loss of neurons within the cerebral cortex and subcortical nuclei.[6]

The worldwide prevalence of prion diseases is estimated at approximately 1-2 cases per million people annually.[7] However, the ability to arrive at realistic estimates through active global surveillance is limited by the propensity for diagnostic delays in countries where resources for the diagnosis of prion disease are limited or nonexistent. For example, Japan and European countries rely on specialized reference laboratories or active national surveillance programs to ensure that cases are identified uniformly. In contrast, India and lower- and middle-income countries face system-specific challenges, such as poor clinician awareness, a lack of molecular diagnostic infrastructure, and underreporting of unusual dementias.[8] These challenges limit our understanding of the prion disease burden and hinder the development of effective context-specific clinical responses.

The current diagnostic methodologies include a clinical assessment coupled with MRI, EEG, CSF biomarkers, and modern protein amplification techniques such as RT-QuIC.[9] Many hospitals in India lack easy access to these diagnostic tools; therefore, prion diseases are often mistakenly diagnosed as other types of dementia or mental disorders. Since there are no therapeutic options that can halt the disease process as of now, most of the management will be palliative. A quick and correct diagnosis is even more important in this scenario.

Innovations in proteomics, gene- and RNA-based therapeutics, and diagnostics with the aid of artificial intelligence show unparalleled opportunities to reshape the treatment of prion diseases.[10] Furthermore, such efforts could be complemented by the establishment of a centralized national epidemiological registry for operationalizing active surveillance and as a basis for implementing early detection and public health response.[11] Diagnostics will need to be bolstered by collaborative interdisciplinary and technological development, as global inequities exist in neurology, with the resources dealing with prion disease efficacy within societies.

Despite the growing body of research in prion biology, there is still an important need for a contemporary and unified review that covers the rapid development of diagnostic technology, growing uncertainties in global disease detection, and pressing challenges to clinicians in areas where diagnostic resources are scarce. Knowledge of prion diseases is often stored in a fragmented manner in many studies, clinical case reports, and surveillance documents, limiting researchers, neurologists, and stakeholders in public health from accessing a unified understanding of contemporary developments.[11] Further complicating an understanding of prion diseases means that they remain wholly underdiagnosed and misdiagnosed, especially in low- and middle-income countries. In the absence of synthesis and unified assessment of advances and uncertainties, stakeholders' ability for informed clinical decision-making, early detection,

and healthcare systems to support a context-specific therapeutic path remains inhibited. An updated review that examines molecular mechanisms, diagnostic technology changes, and healthcare systems is particularly needed and timely.

While much of the previous reviews centered on prion propagation mechanisms, strain biology, or epidemiological trends in high-income countries,[12] few have examined the intersection of contemporary therapeutics, next-generation diagnostics, and health-system inequities in a holistic format. Furthermore, most of the identifiable reviews do not discuss the potential application of disruptive innovations (e.g., AI diagnostic pipelines, gene- and RNA-targeted therapeutics, and sophisticated proteomics protocols) in context(s) lacking the infrastructure needed for conventional prion testing. This review aims to add to the body of literature by synthesizing the advances in science and the diagnostic/surveillance challenges in India and other resource-constrained settings, contributing an inclusivity and a translation perspective that isn't well captured through earlier literature.

2. MECHANISMS OF PRION PATHOGENESIS

Prion diseases are distinct among neurodegenerative disorders because of the provocative nature of their etiology: while not a virus, bacterium, or any other conventional infective agent, prions consist solely of a misfolded host‑encoded protein. The central substrate is the cellular prion protein (PrP^C), which under pathological conditions converts to a misfolded, aggregation‑prone isoform (PrP^Sc). In general, the events that follow the molecular conversion of PrP^C to PrP^Sc include subsequent self‑aggregation, strain diversity, and an eventual neurotoxic consequence, and these events define prion pathogenesis. Here, we will discuss (i) the molecular conversion of PrP^C to PrP^Sc; (ii) genetic factors, specifically the PrP encoding gene (PRNP), that contribute to susceptibility or phenotype; (iii) the biologically hapless properties of prion protein aggregation and strain variability that contribute to disease heterogeneity;[13] and (iv) what these molecular and cellular events mean in terms of clinical and neuropathological outcomes and diagnostic issues.

2.1 PrP^C

The fundamental process at the base of prion disease is the conversion of cellular prion protein, or PrP^C. This mainly α-helical protein is attached to the outside of the plasma membrane through a glycosylphosphatidylinositol (GPI) anchor into the protease-resistant, β-sheet variant PrP^Sc.[14] Within the scientific literature, the conversion of PrP^C to PrP^Sc is commonly elucidated through the templated misfolding, or seeding model, that is based on existing molecules of PrP^Sc serving as conformational templates to encourage PrP^C to be refolded into the misfolded pathogenic form of protein.[15] [16] Through templated misfolding, prion disease depends on exponentially propagating the misfolded PrP^Sc proteins and the transmissible nature of prion disease.[17]

Multiple considerations shape the conversion process. PrP^Sc tends to aggregate, forming oligomers, fibrils, or plaques, which are more resistant to proteolytic digestion than the more soluble, α-helical form of PrP^C.[18] Conversion is favored in particular cellular microenvironments, especially within lipid-raft microdomains and during endocytic trafficking, which impacts both efficiencies of conversion and clearance.[19] Co-factors such as glycosaminoglycans, lipids, and nucleic acids can also modify templating efficiencies and their effects on propagating species barriers and strain-dependent propagation. Prion

pathogenesis is also influenced by the balance between loss of normal PrP^C function (including roles in synaptic maintenance, metal ion homeostasis, and neuroprotection) and toxic gain-of-function actions arising from PrP^Sc aggregates.[19] Accumulation of misfolded protein generates profound stress on the cellular mechanisms of proteostasis, such as chaperones, the ubiquitin-proteasome system, and autophagy-lysosomal pathways, which can further influence the onset and progression of the disease.[19]

2.2 Role of the PRNP gene

Genetic diversity in the PRNP gene, which encodes the prion protein, significantly influences the susceptibility, clinical manifestation, and course of human prion diseases. The PRNP gene is located on chromosome 20p13 and encodes a 253-amino-acid precursor protein that is post-translationally modified to give rise to the cellular prion protein, PrP^C. PrP^C is moved to the surface of neuronal cells, where it plays important roles in the body, such as controlling synaptic plasticity, keeping myelin stable, and affecting circadian rhythms.[20] These important roles show how important PrP^C is for normal neuronal physiology and what happens when its shape or expression changes. Approximately 10-15% of human prion diseases are familial, through autosomal dominant mutations in PRNP that stimulate it to disorder or mutate from a native conformation to PrP^C stably, reducing the energy barrier for misfolding into pathogenic isoform PrP^Sc. Of these mutations, the E200K amino acid substitution is the most common cause of familial Creutzfeldt-Jakob disease (fCJD) worldwide. In contrast, the D178N substitution is unique in that it could cause either fCJD or fatal familial insomnia, depending on whether the codon 129 polymorphism is present in the same allele (Table 1).[16] Another significant mutation, P102L, is tied to Gerstmann–Sträussler–Scheinker syndrome (GSS), a prion disorder that is characterized by progressive cerebellar ataxia and cognitive decline. Normally, these mutations lead to a greater propensity of causing misfolding of PrP^C, changes in its cellular trafficking, or a reduction in clearance mechanisms for prions, respectively, accelerating both the onset and progression of prion disease. Besides pathogenic mutations, polymorphisms in PRNP, whether common or rare, have substantial impacts on risk and disease expression. The methionine/valine polymorphism at codon 129 is the polymorphism that has been most studied, as homozygosity at this codon (Met/Met or Val/Val) leads to a greater risk for sporadic and variant forms of Creutzfeldt–Jakob disease, as well as modifying incubation periods, age of onset, and disease phenotype. Alternatively, other rare polymorphisms, like Gly127Val, have been suggested to confer resistance against prion disease in affected populations with a history of kuru exposure in Papua New Guinea. Structural and computational studies suggest that these protective polymorphisms stabilize loops, which are critical in the structure of the PrP^C molecules,[20] thus resulting in a lower efficiency of PrP^C to PrP^Sc conversion and exemplifying how a subtle change in sequence can modulate risk of pathogenesis.

Table 1. Key PRNP mutations and polymorphisms and their clinical implications.

Variant	Type	Disease Association	Mechanistic Effect	Population Notes
E200K	Pathogenic mutation	Familial CJD	Destabilizes PrP^C structure; lowers energy barrier for misfolding	Most common fCJD mutation worldwide
D178N	Pathogenic mutation	fCJD or FFI	Alters PrP^C folding; phenotype dependent on codon 129 genotype	Cis-interaction with codon 129 determines clinical manifestation
P102L	Pathogenic mutation	GSS	Promotes misfolding and fibrillogenesis	Rare, associated with progressive cerebellar dysfunction
Codon 129 (M/V)	Polymorphism	Sporadic and variant CJD	Modulates PrP^C–PrP^Sc templating efficiency; influences strain selection	Homozygosity (Met/Met or Val/Val) increases susceptibility
Codon 127 (G/V)	Polymorphism	Kuru resistance	Stabilizes critical loops; impedes conversion	Observed in populations exposed to kuru (Papua New Guinea)

Biochemical characteristics of the pathogenic isoform PrP^Sc influence the relationship between genotype and phenotype. For example, the protease cleavage pattern, ratios of glycoforms, and conformational stability of PrP^Sc interact with the host's genotype to determine clinical sub-phenotypes, distribution in the brain, and the rate of disease progression.[20] Moreover, the overall expression level of neural tissue-associated PrP^C affects disease kinetics, with higher levels of PrP^C expression promoting earlier onset of disease in experimental models. The sequence variations of PrP^C also affect the "species barrier" because the transmission of prion disease depends on compatibility in the primary sequence of amino acids.[20]

These observations, in summary, support the role of PRNP, the prion-related gene, in the pathogenesis. Mutations probably make the disease much worse due to the lower stability of PrP^C, which accelerates the oligomerization process, leading to the pathological form of PrP. The polymorphisms may confer either susceptibility or resistance, depending on their structural and functional implications. Overall, the interplay between the genotype of PRNP, the biochemical properties of PrP^Sc, and the cellular environment accounts for the diverse manifestations concerning disease onset, progression, clinical

phenotype, and neuropathology.[21] Thus, these genetic elements are crucial to understanding the mechanisms of prion pathogenesis and important for guiding diagnosis, prognosis, and future approaches to treatment.[22]

2.3 Aggregation Behaviour and Strain Diversity

After conversion, PrP^Sc molecules aggregate into oligomers, fibrils, and larger aggregates. These aggregates exhibit varied behavior, forming the basis for the phenotypic diversity of prion diseases. Prion strains are distinct conformational variants of PrP^Sc that replicate correctly while retaining different biochemical and pathological properties.[23,24] More than their larger fibrillar counterparts, small soluble oligomers seem more neurotoxic and more adept at propagation along neural circuits, though they may spread more slowly.[25,26]

Strain-specific conformations also have distinctive protease resistance profiles, ratios of glycoforms, solubility, and neuroanatomic targeting that encode information regarding disease tropism and progression.[26] There is an interaction between strain identity and host genotype, particularly with regard to codon 129 status that influences disease phenotype; this interaction explains why the same inoculum yields differences in clinical course.[26] In many acquired prion diseases, peripheral amplification preceded invasion of the central nervous system (CNS) (i.e., lymphoid tissues). The size and conformation of the aggregates determine the kinetics of neuroinvasion; in general, oligomeric seeds are more capable of CNS entry than larger fibrillar assemblies.[26] Together, aggregation and strain diversity are important contributors to clinical heterogeneity.

2.4 Clinical Implications

The downstream effects caused by the conversion and aggregation of molecules lead to significant neurodegeneration and related neuropathology. The classical hallmarks of these diseases will often include spongiform vacuolation, neuronal loss, astrogliosis, microgliosis, and PrP^Sc deposition in plaques or diffuse aggregates. In clinical cases, synaptic dysfunction, the loss of dendritic spines, and early degeneration of the synapse may precede full neuronal death. When placed under abnormal cellular conditions, PrP^Sc assemblies will alter synaptic transmission while simultaneously inducing mitochondrial dysfunction, oxidative stress, excitotoxicity, and endoplasmic reticulum stress responses.[26] Clinical manifestations vary depending on strain-host interactions and can include rapidly progressive dementia, myoclonus, cerebellar ataxia, sleep disturbances, and akinetic mutism, with interventions potentially having a prolonged incubation time (often years) in the case of inherited or acquired forms, while post-symptomatic disease progression is rapid (death in a few months).

Diagnosis continues to be difficult because the accumulation of PrP^Sc may not be present visually until the lesions appear, and even then, PrP^Sc may be limited to regional aggregates. Current approaches, especially involving cerebrospinal fluid RT-QuIC, 14-3-3 protein detection, MRI, and EEG, have enhanced the detection ability but still have limitations with early-stage sensitivity and subtype differentiation (e.g., vCJDD vs. sCJD).[26] Therapeutic options are in their infancy or more untenable because of the speed of progression of these proteins, along with their individuality in attacking host

proteins and existence within strains. Treatments would require achieving the complete inhibition of PrP^C conversion, complete clearance of v-CJD PrP^Sc seeds, blockade of propagation production, and protection of healthy neurons; however, no curative strategies are available, and in time they act to ensure that further seeds of infection are propagated and not cleared.

3. EPIDEMIOLOGY & INDIAN RESEARCH LANDSCAPE

Prion diseases, also known as transmissible spongiform encephalopathies (TSEs), are rare but invariably fatal neurodegenerative disorders caused by the accumulation of misfolded prion proteins. Globally, the incidence of prion diseases is estimated at one to two cases per million population per year, with sporadic Creutzfeldt–Jakob disease (sCJD) accounting for the majority of cases.[26] Familial forms, resulting from inherited mutations in the PRNP gene, and variant or iatrogenic forms, associated with exposure to contaminated biological material or medical procedures, are less common. Risk factors include advanced age, specific PRNP genotypes, particularly homozygosity at codon 129, and prior exposure to contaminated tissues or surgical instruments. Historical dietary or cultural practices, such as endocannibalism, have contributed to outbreaks, including kuru in Papua New Guinea.

3.1 Global Epidemiology and Risk Factors

Sporadic CJD usually occurs in people in their sixth or seventh decades of life, with rapid progression, and median survival is typically less than one year. Familial prion diseases account for about 10–15% of cases and are linked to specific PRNP mutations, such as E200K, D178N, and P102L, that instantiate instability in PrP^C and reduce the kinetic barrier to misfolding. Variant CJD, which was reported for the first time by investigators in the United Kingdom, has implicated a dietary exposure to bovine spongiform encephalopathy-contaminated meats and reaffirms both environmental and zoonotic risk factors.[26] Other factors, such as PRNP codon 129 homozygosity, age, and possibly chronic inflammation, would also be salient in susceptibility to developing disease and in the propagation of disease.

3.2 Prion Diseases in India

The epidemiology of prion diseases in India is not well characterized. Sparse case reporting, limited public and clinical awareness, and the lack of a national registry make it difficult to estimate true incidence or prevalence. As of this date, only a few dozen cases of sporadic and familial prion diseases have been formally reported, primarily from tertiary care centers and neuropathology laboratories in urban settings.[27] The reports indicate that the demographic profile of Indian patients with prion disease is similar to international characteristics, with a median age at incidence in the sixth to seventh decade and without a strong gender predilection. Familial cases are rare but have been reported, typically in association with PRNP codon 129 or codon 127 polymorphisms. These reports are anecdotal, however, as systematic surveillance initiatives and molecular epidemiologic studies are still lacking. The current conclusions are limited by the small number of case reports, underdiagnosis, limited surveillance infrastructure, and small number of patients within each cohort.

3.3 Risk Factors and Environmental Contributors in India

Apart from genetic susceptibility, case reports from India indicate that environmental and iatrogenic factors might have also played a role. In rare cases, a neurosurgical procedure or the use of poorly sterilized instruments could have triggered the illness; however, there is limited literature on record about such incidents.[27] Sociocultural factors, including dependence on and restricted acceptance of traditional medicine, alongside the body's refusal to undergo postmortem examination, further impede the recognition and reporting of these cases. In contemporary India, dietary consumption of prion-infected tissues is no longer a significant factor; however, a specific dietary or cultural practice may still account for sporadic cases in certain communities. These factors show how genetic, environmental, and sociocultural factors work together to cause disease in India.[28]

3.4 Clinical Case Studies in India

Several case reports from Indian institutions (National Institute of Mental Health and Neurosciences [NIMHANS] and All India Institute of Medical Sciences [AIIMS]) have detailed clinical and molecular features (Table 2). Patients usually present with rapidly progressive dementia, myoclonus, cerebellar ataxia, and behavioral changes, eventually progressing to akinetic mutism in a few months.[28] A diagnosis is bolstered by cerebrospinal fluid (CSF) biomarkers (14-3-3 protein, total tau, and RT-QuIC assays) and electroencephalography (EEG) showing periodic sharp-wave complexes in the setting of magnetic resonance imaging (MRI) that demonstrates diffusion-weighted hyperintensities in the cortical ribbon, caudate, and putamen.[28,29]

The PRNP genotyping of these cohorts showed that codon 129 polymorphisms influenced susceptibility as well as the pace of disease progression: homozygous individuals (MM or VV) have a heightened risk of more aggressive disease, while codon 127 (G127V) variants may create partial resistance.[29] When the PRNP genotype is combined with PrP^Sc biochemical profiling, which includes ratios of glycoforms and protease resistance, preliminary correlations with clinical subtypes are found. However, there is a limited amount of strong data in Indian populations. Despite these interesting diagnostic methods, they have several problems. The postmortem examination, considered a gold standard, is rarely done owing to cultural and logistical reasons and may lead to underreporting of the disease. Initial manifestations of the disease may also give subtle imaging changes, thus making preclinical diagnosis difficult.

Table 2. Reported human prion cases in India with diagnostic and genotype data.

Data compiled from Mehra *et al*., Pradhan *et al*., Singh *et al*.,[29] and institutional case reports.

Year	Location	Case Type	Age (yrs)	Gender	PRNP Genotype	Diagnostic Method	EEG Findings	MRI Findings	Outcome
2010	Karnataka	sCJD	62	M	MM at codon 129	CSF 14-3-3, MRI	Periodic sharp-wave	Cortical ribbon hyperintensity	Deceased, 6 months
2012	Delhi	fCJD	45	F	D178N + MM	RT-QuIC, MRI	Periodic complexes	Basal ganglia hyperintensity	Deceased, 8 months
2015	Uttar Pradesh	sCJD	59	M	MV	MRI, EEG	Nonspecific slowing	Caudate hyperintensity	Deceased, 10 months
2017	Kerala	fCJD	51	F	P102L + MV	MRI, CSF 14-3-3, PRNP seq	Periodic sharp-wave	Cortical and basal ganglia	Deceased, 9 months
2018	Telangana	sCJD	64	F	MM	MRI, RT-QuIC	N/A	Cortical ribbon	Deceased, 7 months

4. DIAGNOSTIC MODALITIES AND OUTCOMES

Typically, the diagnostic modalities available in India follow international standards. These include:

- CSF Biomarkers - 14-3-3 protein, total tau, and RT-QuIC assays. RT-QuIC has shown significant sensitivity (~85–95%) and specificity (~99%) in Indian cohorts.
- EEG - at later stages, we can see periodic sharp-wave complexes; however, the sensitivity is limited (~60–70%) in the early disease stage.
- MRI - diffusion-weighted imaging and FLAIR sequences usually show hyperintensities in the cortical ribbon, caudate, and putamen. MRI abnormalities were observed in roughly 80% of reported Indian cases at diagnosis. [29]

RT-QuIC assays have exhibited high sensitivity and specificity for PrP^Sc seeding detection in CSF or nasal brushings. MRI is an important diagnostic modality that can identify hyperintensities, although EEG can support diagnosis in later stages. 14-3-3 protein and tau are biochemical CSF markers that assist impoverished diagnostic confidence in prion disease detection; however, these biochemical markers do not differentiate all subtypes.

Therapeutic interventions in India discussed are primarily focused on providing supportive care to address symptoms, including myoclonus, sleep disturbances, and behavioral disturbance, as there are no disease-modifying therapies available, and prognosis is poor, as the median survival from initial onset of the disease is typically <12 months. In rare cases, early recognition and provision of multidisciplinary supportive care. Rarely, early detection and multidisciplinary supportive care may modestly improve quality of life, but clinical outcomes are generally fatal.[29]

4.1 Treatment Strategies and Clinical Outcomes

Therapeutic interventions in India remain supportive, focusing on symptomatic relief. Myoclonus and seizures are managed with benzodiazepines or antiepileptics, sleep disturbances (notably in fatal familial insomnia) are addressed with sedatives and behavioral strategies, and behavioral and psychiatric symptoms are treated with psychotropic medications as needed. No disease-modifying treatments exist. Clinical outcomes are uniformly poor, with median survival post-onset typically under 12 months. Early detection and multidisciplinary supportive care may modestly improve quality of life but do not alter mortality.

4.2 Research Landscape and Challenges in India

Research on prion diseases in India is expanding slowly. Recent studies have explored PRNP polymorphism to identify population-specific susceptibility patterns, molecular characterization of PrP^Sc strains in sporadic and familial cases, and biomarker development, particularly RT-QuIC and CSF proteomics, for early detection. Collaboration with international centers has allowed access to RT-QuIC and advanced neuropathology techniques.[29] Issues are a lack of national surveillance, limited clinician awareness, a limited diagnostic infrastructure for sites declustered outside of urban centers, and societal and cultural issues regarding post-mortem confirmation. Building epidemiology capacity, studying genetics and biomarkers, and raising clinician/public awareness are areas in need of refinement in India for advances in prion scientific understanding/epidemiological rank, and prion patient care. Building strong research and surveillance capacity is critical. A system to capture clinical data, imaging, and biomarker data would be critical to understanding the true incidence, being able to study genotype–phenotype correlations, and identifying at-risk cohorts. Linking genetic studies to clinical and imaging phenotypes has the opportunity to study modified ways to detect and/or treat prion disease earlier.[29]

5. DIAGNOSTIC INNOVATIONS: AI & PROTEOMICS

Identifying prion diseases remains one of the biggest hurdles in the fields of neuroscience and infectious diseases. Prion diseases are caused by the normal prion protein (PrP^C) misfolding into its infectious isoform (PrPSc), leading to an irreversible series of events resulting in significant brain damage. Due to the rapid progression of the disease and the priors often resembling other forms of dementia, early and accurate diagnosis is extremely difficult. MRI imaging, cerebrospinal fluid (CSF) analysis, and electroencephalograms (EEGs) can offer insights, yet their sensitivity and specificity remain ambiguous.

Recently, new methods that combine artificial intelligence (AI) with proteomics show a lot of potential for improving the early detection, accuracy, and understanding of prion disease.

5.1 Current Diagnostic

The diagnosis of prion diseases primarily relies on a combination of clinical assessment, neuroimaging, and laboratory-based tests. Among others, the Real-Time Quaking-Induced Conversion (RT-QuIC) assay and Protein Misfolding Cyclic Amplification (PMCA) are considered most robust for detecting the disease-associated misfolded prion protein, PrPSc, in the cerebrospinal fluid (CSF) or other tissues.[30] The RT-QuIC detects small amounts of misfolded prion protein and amplifies it to levels detectable by standard assays. PMCA mimics the natural conversion of normal prion proteins (PrP^C) to a pathogenic state. In addition, MRI often shows characteristic patterns of hyperintensities in the caudate nucleus, putamen, or cerebral cortex. At the same time, EEG can reveal periodic sharp wave complexes highly suggestive of Creutzfeldt-Jakob disease (CJD).[30] While all these advances have improved the ability to confirm prion diseases, they tend to be best at confirming diagnoses after substantial neurologic advance and damage have taken place.

5.2 Limitations

While advancements in diagnostic tests have been made, there are still limitations. RT-QuIC and PMCA are only performed in highly specialized laboratories with trained personnel and state-of-the-art equipment, requiring a considerable amount of timely and monetary resources.[32] Additionally, these tests remain sensitive but are still susceptible to false-negative test results during early and/or atypical cases due to limited amounts of detectable PrPSc. Because the neuroimaging and EEG techniques are noninvasive, they also lack critical and sufficient sensitivity to detect prion diseases in the early stage (or variant prion disease).[33] These limitations highlight the need for diagnostic systems that are quick, scalable, and accessible in high- and low-resourced settings.

5.3 AI-Based Diagnostic Systems

AI has potential to help in the diagnosis of patients by doctors as it finds patterns in data not easily accessible to human experts. The AI systems can go through MRI scans, EEG signals, and clinical data on prion disease to detect minute changes associated with it. Additionally, you can train ML and deep learning models, such as CNN, using existing knowledge for identifying structural and signal changes in the brain. Examples include characteristic spongiform patterns, thalamic or cortical signal changes, and cerebellar shrinkage seen commonly in CJD patients. Recent studies on ML-based MRI analysis have demonstrated that this can distinguish sporadic CJD from other rapidly progressive dementias with an accuracy of over 90%.[33] Besides this, AI has been able to diagnose the disease at a very early stage, just before the emergence of strong symptoms, based on the fusion of data from different imaging modalities, including DWI and measurement of gray matter volume. Thirdly, AI has also analyzed EEG recordings and is capable of autonomously identifying wave patterns in the EEG specific to prion etiology, thus showing immense potential in paving the way for faster and noninvasive screening of the disease.[33] AI can also help the physician in other ways: algorithms using NLP may look at patient records and see the worsening of symptoms and lab results in order to point toward possible prion cases. These capabilities

may be extended to facilitate evaluation of laboratory tests like the RT-QuIC assay, a highly sensitive method for detecting prion protein seeding activity, to aid in diagnostic and early intervention advice.

5.4 Proteomics and Prion Biomarkers

It has, therefore, emerged that proteomics offers a viable approach to surmount these challenges through the detection and quantification of protein biomarkers associated with prion pathology. Basically, prion diseases arise from protein misfolding; thus, deep profiling of proteins may lead to the identification of molecular signatures that distinguish individuals affected by prion diseases from healthy individuals. Given that prion diseases are a consequence of abnormal protein folding, proteomics, the large-scale study of proteins, provides direct insight into a disease at the molecular level. For a variety of prion diseases, prion studies utilizing sophisticated methods such as mass spectrometry (MS) and liquid chromatography (LC-MS/MS) have reported that certain proteins with distinct properties are enriched in prion disease when compared with other prion diseases. For example, several proteins, including 14-3-3, tau, neurofilament light chain (NfL), and clustering (CLU) in CSF, have been associated with neuronal damage in CJD.[34] Though the RT-QuIC assay remains one of the most reliable tests for the presence of PrPSc, it greatly improves in performance advantage when coupled with proteomic analysis.[35] Moreover, proteomic approaches can provide information on subtle post-translational modifications (PTMs) of proteins, such as glycosylation or oxidation, that may help distinguish infectious PrPSc from the normal form and provide additional diagnostic information.[36]

Recent technological developments have improved the precision with which proteomic testing is done. Advanced techniques include targeted proteomics, immunoprecipitation-MS, or nanopore-based detection, allowing precise identification of PrPSc and some post-translational modifications, such as glycosylation or oxidation.[37]

5.5 Combining AI and Proteomics

The integration of artificial intelligence and proteomics is a significant step forward in precision diagnostics. By feeding ML models proteomic data, such as protein level, folding, pattern, and post-translational modification, scientists can teach them to recognize the molecular signature of prion diseases. For instance, it has been possible for supervised machine learning models to distinguish between CJD, Alzheimer's, and frontotemporal dementia based solely on CSF proteomic data.[38] Even unsupervised clustering can reveal new prion disease variants that could point to distinct strains or modes of disease transmission. AI algorithms can analyze WSI data derived from brain biopsies or autopsy specimens for the detection of spongiform changes and PrPSc deposits more consistently than human observers.[39] Similarly, deep learning models, mainly CNNs, were employed to evaluate MRI data of patients who can identify/distinguish prion diseases from other dementias with >90% accuracy. AI also informs biomarker discovery. For example, algorithms such as random forests and support vector machines (SVMs) evaluate hundreds or thousands of protein points to determine which of these proteins differentiate healthy subjects from proteinopathy patients.[39] When proteomics is combined with transcriptomics or metabolomics, it helps us understand the pathology of prions even better.

AI helps identify biomarkers in the still-developing field of proteomics by quickly analyzing large data sets and focusing on the combination of proteins that best predict a disease. Support vector machines and

random forest classifiers, for example, have uncovered proteomic profiles contributing to distinguishing prion-positive cases before a clinical diagnosis is normally possible. A variety of AI-enhanced RT-QuIC analysis technologies have been developed, capable of automatically identifying fluorescence curve patterns, hence more efficient and eliminating false positives.[40] [41] Once positive curves are determined, further diagnostic analysis employing AI-driven methods can yield positive results faster. Neural networks can examine and sort curve patterns to eliminate false positives further and possibly identify prion strains. Generally speaking, adding AI can help speed diagnostic tests and facilitate the standardization and scaling of experiments in the same way for all laboratories. The combination of AI and proteomics has potential to form a diagnostic model based on data, but at the same time, it is compatible with biology.

5.6 Potential in India

In India, where prion diseases are uncommon yet sporadically documented, these diagnostic advancements could significantly influence public health. Most hospitals in cities have MRI and EEG machines, but only a few research institutes have RT-QuIC and proteomic machines.[40] [41] If India is able to develop AI-assisted diagnostic workflows, India would be able to scale solutions that integrate imaging and molecular data without needing advanced infrastructure at every site. For example, cloud-based AI systems could assess MRI images or digital whole slide imaging (WSI) images from several hospitals and return rapid probabilistic diagnoses to physicians. Increased access to expert-level review would improve diagnostics. For rural primary health centers (PHC), portable biosensing devices with AI processing would enable screening with small-volume CSF or blood samples. These systems could allow for early detection, referral, and tracking of potential prion disease cases. Early triaging of prion disease is critically important for control of disease transmission, epidemiological tracking, and messaging across a very large country.

5.7 Challenges and Future Outlook

While the progress is exciting, there are numerous hurdles remaining before these technologies can be adopted into practice. First, prion diseases are quite rare, which will affect the ability to pull large data sets that are also very diverse with different populations, patient ages, sex and gender distributions, and comorbid conditions into an AI model. Second, proteomic workflows are performed with slightly different approaches across laboratories, which can affect reproducibility. Third, ethical issues concerning patient data must be considered before AI-based diagnostics can be adopted. Future directions include creating federated AI systems, which can allow multiple research centers to train a shared diagnostic model without sharing sensitive patient data.[58] Future directions could also include strategies to develop standardized proteomic workflows and open-access databases to make biomarker research reproducible and transparent.

5.8 Cross-Disease Proteinopathy Insight

Neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD), have something in common: the accrual of pathogenic proteins that misfold, disturbing cellular homeostasis and neuronal function. While prion

diseases were once thought of as unique because of their transmissible misfolded protein forms, there has been a growing amount of evidence that many neurodegenerative diseases possess "prion-like" features because of templated aggregation, intercellular dissemination, and the propagation of toxic states.[43,44] This cross-disease proteinopathy has redefined our contemporary conception of neurodegeneration, moving it from a compartmentalized concept of pathologies to a continuum of pathological molecular events. Cross-disease proteinopathy in Prion diseases are characterized by the presence of misfolded prion protein (PrP^Sc) in association with other misfolded proteins that are associated with other neurodegenerative diseases. Prion diseases are defined most simply by the conversion of the normal cellular prion protein (PrP^C) into its pathogenic form and there is increasing evidence that other proteinopathies are often present in affected brains. Investigations have found deposits of hyperphosphorylated tau, amyloid-β (Aβ), α-synuclein and TAR DNA-binding protein 43 (TDP-43) in patients with sporadic, genetic, and acquired prion diseases. These proteins can interact in a cross-seeding manner, so that one misfolded protein can promote the aggregation of another protein, which leads to the acceleration of neurodegeneration. For instance, tau pathology is a frequent feature of Creutzfeldt–Jakob disease (CJD) and Gerstmann–Sträussler–Scheinker syndrome (GSS); and Aβ plaques can be present in some inherited prion diseases in addition to PrP amyloid deposits. Clinical heterogeneity is caused by the presence of multiple proteinopathies; these have an impact on clinical course and on the neuropathological diagnosis. Moreover, cross-disease proteinopathy is consistent with the notion that common molecular mechanisms such as failure to clear proteins, neuroinflammation, oxidative stress, and synaptic dysfunction contribute to many neurodegenerative diseases. Understanding these interactions in prion diseases could lead to a better understanding of the common mechanisms of protein misfolding and propagation that could be useful when developing therapeutic strategies against neurodegeneration.

6. MOLECULAR MECHANISMS OF PROTEIN MISFOLDING

At the molecular level, proteins linked to certain diseases experience conformational alterations that result in self-replicating behavior, akin to the prion protein (PrP^Sc). Amyloid-β and tau in AD, α-synuclein in PD, TDP-43 and SOD1 in ALS, and mutant huntingtin in HD can all act as seeds for the misfolding and aggregation of their normal counterparts.[45] Misfolded proteins undergo propagation into neuronal populations via multiple different mechanisms, including exosome-mediated transport, tunneling nanotubes, and trans-synaptic transmission.[46] [47] The cellular responses to protein aggregation are conserved through neurodegenerative disease states. Amyloid protein aggregates lead to endoplasmic reticulum stress and initiation of an unfolded protein response,[48] impair autophagy and proteasomal degradation, elicit mitochondrial dysfunction, and induce neuroinflammation through microglial activation.[49-51] Given this conservation across neurodegeneration, it follows that the pathological mechanism of protein aggregates is a common response leading to progressive neurodegeneration rather than a consequence of their disease-specificity.[52]

6.1 Co-pathology and Molecular Crosstalk

An important consideration in studies of pathological processes across diseases is the commonality of co-pathologies. Co-pathologies occur when multiple misfolded proteins exist in the same brain. For example, as many as 60% of Alzheimer's disease patients will have at least some inclusions of

α-synuclein or TDP-43,[53] and experimental evidence describes α-synuclein-tau cross-seeding *in vitro* and *in vivo*.[54,55] Similarly, experimental work has shown that PrP^Sc may modulate tau phosphorylation and accelerate amyloid-β deposition in transgenic models, suggesting possible molecular crosstalk among prion and non-prion proteinopathies.[56] The intersection of proteinopathies may affect disease course, clinical phenomenology, and treatment engagement.

6.2 Integrated Strategy for India

Prion diseases continue to persist in India without recognition. Inadequate diagnostic resources, fragmented reporting, and limited clinical expertise are the major challenges in identifying prion diseases, according to a source.[56] We propose the establishment of a National Prion Disease Surveillance and Research Network (NPDSRN) to address these challenges. The NPDSRN would provide a centralized resource and help link tertiary hospitals, diagnostic laboratories, and research institutions in monitoring cases, conducting molecular characterization, and carrying out genomic analysis. Programs such as the ICMR and NIV can support this initiative through the provision of the much-needed guidelines and infrastructure. Apart from establishing an NPDSRN, a national biobank for human cerebrospinal fluid, brain tissue, and genomic samples would be useful. This may facilitate exploratory research on multiple omics that shall aid in the identification of region-specific variants of prions, co-pathologies, and molecular biomarkers according to Patel & Sharma. Establishment of standardized operating procedures on sample collection, storage, and sequencing would facilitate ease in replication and reproducibility of multi-site research in several research studies.

AI and ML can revolutionize the diagnosis of prion diseases, which often present like Alzheimer's or Parkinson's disease. AI-powered proteomics and whole slide imaging analysis can be conducted on neuropathology datasets for the automation of lesion detection and quantification of protein aggregates.[57] These modalities, along with integrated longitudinal clinical and neuroimaging data, will lead to improved differential diagnosis and disease staging. Integration of population-specific genomic and epigenetic data into machine learning algorithms in next-generation sequencing techniques may yield a unique diagnostic signature for the Indian population. Neurologists, pathologists, molecular biologists, and computational scientists need to come together to develop a precise, scalable, and affordable complex diagnostics process that caters to the needs of the Indian healthcare system.

Gene- and RNA-based methods represent the new frontier in prion therapeutics. Methods such as RNA interference, antisense oligonucleotides, and CRISPR-Cas9 genome editing have shown capabilities to downregulate PRNP expression and neurotoxicity. Next-generation base editing and prime editing techniques can be modified to identify populations associated with PRNP mutations in Indian genomic datasets. In furtherance of translational relevance, preclinical models derived from Indian genotypes can be generated in order to study therapeutic efficacy and off-target effects.[58] Indeed, India's biotechnology ecosystem is ready to facilitate this translation pipeline through innovation programs initiated by the government.

For a research ecosystem to be sustainable, there has to be an integrated data backbone. The NPDSRN will facilitate clinical case tracking in real time and genotype-phenotype integration with trend

monitoring. Cross-disease cohorts are also established, comparing prion disorders with Alzheimer's, Parkinson's, and other neurodegenerative diseases in search of common molecular pathways and treatment targets. The data originating from this registry must be standardized. To convert it into a secure national database that facilitates open-access analytics and multi-omics research, interoperable standards should be employed. Collaboration with universities and national supercomputing centers will accelerate biomarker discovery and the development of computational models.

A phased implementation approach has been suggested to make research useful in the clinic. Pilot programs at tertiary hospitals, especially national neuroscience hospitals and branches of AIIMS, need to be set up to look into how to use AI-assisted analyzers, set up plans for sharing data, and put diagnostic workflows into action.

After changes are made, outreach to Primary Health Centers (PHCs) will make it easier to spot symptoms early and refer people to the right place. Other similar projects should include training modules for neurologists and lab technicians, certification of BSL-3 testing facilities, and adding prion disease awareness to both medical and paramedical curricula. These strategies will guarantee the attainment of diagnostic scalability and biosafety protocols.

7 CHALLENGES AND FUTURE DIRECTIONS

7.1 Diagnostic and Epidemiological Limitations

The main problem with prion disease research and treatment in India is that it is hard to tell what is wrong with someone. The clinical manifestations of prion diseases, irrespective of their IOM classification, such as rapid cognitive decline, ataxia, and behavioral disturbances, closely resemble those of Alzheimer's, Parkinson's, and frontotemporal dementias. As a result, dementia is often misdiagnosed or not identified promptly. Only a few labs with special skills can do confirmatory tests like real-time quaking-induced conversion (RT-QuIC),[59] western blot identification, or sample identification of PrP^Sc.

7.2 Infrastructural and Funding Constraints

The focus of India's research capacity on neurodegenerative diseases is tilted towards Alzheimer's and Parkinson's disease and does not significantly cover prion diseases in the realm of national funding. There is a critical lack of BSL-3 laboratories necessary for safe working with infectious prion material and a limited number of trained neuropathologists in prion-specific histopathology and molecular diagnostics, which is a challenge for establishing preclinical models, pathogen inactivation research, and assay screening, all of which are vital for translation. Furthermore, the lack of cross-institutional and disciplinary collaborations among data scientists, molecular biologists, clinicians, and biotechnologists is limiting the application of computational modeling and AI-based diagnostic algorithms in the real world. India must invest targeted funding calls to agencies like DBT, ICMR, and SERB for prion biology and work with public-private partnerships to develop diagnostic capacity and train students in AI and bioinformatics in a neuroscience curriculum. Regional centers of excellence in neuroinfectious diseases will help accelerate translation and clinical application.

7.3 Ethical, Genetic, and Translational Challenges

As India begins to consider the potential of gene- and RNA-based therapeutic strategies,[59] a number of ethical and translational challenges arise. India also has a vast amount of genetic heterogeneity, which makes it challenging for therapeutics developed in Western populations to be used directly as-is. Different PRNP variants that are regional, as stipulated by the epigenetic regulation and/or environmental cofactors, would require population-specific validation of the human trials' findings before application. In the case of gene-editing potential therapies driven by CRISPR-Cas or base-editing technologies, considerations need to be made concerning off-target effects, germline transmission concerns, and potential ethical concerns with respect to Phase I human trials.

A strong set of rules will be needed to ensure safety, openness, and informed consent. Also, as more people use AI-based diagnostic systems, issues will come up about data privacy and ownership, algorithmic bias, and the possibility of unfair healthcare. Ethical oversight committees ought to possess the authority to evaluate both technological interventions and data-sharing practices to guarantee that the progression of science does not exacerbate the disadvantages faced by already marginalized and underrepresented groups regarding access.

8. FUTURE RESEARCH AND POLICY DIRECTIONS

Future advancements in India's prion research ecosystem should focus on four interrelated priorities:
Creating a biobank and integrated data repository: For population-level research on prion disease, there needs to be one national repository for genomic, proteomic, epigenomic, and clinical metadata. The repository can also help with long-term research, bring together different types of omics data from the same population or from different populations, and make it easier to compare with other diseases caused by protein misfolding, like Alzheimer's and Parkinson's diseases.

More AI-powered neuroimaging diagnostics and the use of proteomics and digital pathology at different levels of healthcare can help find problems earlier, especially in places where resources are limited.

Support next-generation therapeutics: Research on prion disease should concentrate on RNA-based modulation, antisense oligonucleotides (ASOs), and small-molecule inhibitors to influence pathways related to protein folding and aggregation. To help with synthesis problems, prion researchers and Indian biotech companies need to work together more.

Policy change and partners from different fields: To encourage innovation, the government will also need to keep supporting it through dedicated funding programs, ethical data-sharing frameworks, and a faster regulatory regime. Government and policy support would also help the relationships between academia and private industry, the creation of a strong ecosystem for clinical trials, and the development of new award mechanisms to draw young researchers into prion science.

Strategic and Technical Pathways Forward

A formal, multi-tiered strategy for implementation is key to achieving sustainable advancement in prion disease research and management in India: one that includes technological innovation, infrastructure, and ethical governance to facilitate the use of research to practice.

Technological Innovations:

New treatment paradigms must tackle important scientific and engineering problems. Off-target effects in gene editing will need to be reduced through better design of guide RNAs, incorporating high-fidelity Cas variants, and testing for safety over longer periods. The brain's blood-brain barrier limits the delivery of RNA-based therapeutics; nanoparticle and viral vector-mediated delivery systems have the potential to improve bioavailability. AI models cannot risk bias if the training dataset is expanded to include a range of Indian populations and clinical presentations.

Infrastructure:

Nationally, a strong infrastructure is necessary to support innovations in prion disease research and treatment. Biofoundries should be established throughout India to facilitate high-throughput screening in addition to a standardized data pipeline to improve reproducibility and collaboration. A framework for coordinating a national sample collection should be developed to standardize the biobanking and clinical annotation and incorporate genomic data from future collaborative institutional providers and more across future data integration and collaboration. Ultimately, the ability to test the data reproducibly across institutions and bring it into a National Prion Data Grid will support and strengthen the field while linking hospitals and laboratories with researchers.

Ethical and regulatory framework:

This rapid growth of molecular and computational technologies calls for governance that is both simple and clear. The procedures of informed consent must consider genomic sequencing, reuse of data, and AI-based diagnosis. Global ethics guiding gene editing should delineate the boundaries of acceptability for somatic editing and prohibit germline editing. Data protection regulations need to be enhanced for the protection of patient data in multi-omic and AI-driven research studies.

9. CONCLUSION

Prion diseases pose a significant health problem worldwide due to their lethal nature, difficulty in diagnosis, and relative rarity. In order to achieve good control, treatments must be combined with tests and an excellent health system. Gene and RNA therapies, small-molecule stabilizers, and immune-based treatments are promising for possible therapies that could delay or even block the replication of prions. RT-QuIC, amplification assays, and imaging biomarkers all further enable early diagnosis and simultaneous improvement of diagnostic accuracy. However, scientific developments can lead to major health benefits only when supported by a broad system of surveillance, standard reporting, and equal access to diagnostics. Since neurodegeneration through prions is rapid and irreversible,[59] timely diagnosis remains the cornerstone. In India, a general lack of awareness and significant underreporting emphasize

the need for a national framework for addressing prion diseases. Establishment of centralized reference laboratories, extension of neuropathology networks,[59] and compulsory reporting to the National Centre for Disease Control rank among the top recommendations. Training programs in molecular biology, bioinformatics, and neurology would offer a preparatory platform for the country toward new prion challenges. Thanks to investments in genomics, AI-powered diagnostics, and translational research, India's biotechnology sector is growing fast. This is the right time to integrate prion research into bigger neurodegenerative projects. Biomarker discovery, development of therapies, and affordable diagnostic solutions catering to the Indian healthcare system can all be accelerated through facilities like the National Brain Research Centre and international partnerships for data sharing. Employment of India's scientific expertise, technological capabilities, and rich population diversity enables it to position itself at the top globally when it comes to research on rare neurodegenerative disorders. Through its collaborative effort of improving therapeutics, diagnostics, and infrastructure, the strategy followed by India with respect to prion diseases can evolve from problem-solving to prevention, setting an example before the world on how to tackle other rare and complicated diseases.

Author's contributions:
Tisha Sehrawat conceptualised the study, did literature survey, wrote and corrected the manuscript.

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