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Prion diseases and genetic susceptibility

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ABSTRACT

Prion diseases, also known as Transmissible Spongiform Encephalopathies (TSEs), are fatal neurodegenerative disorders caused by misfolding of the prion protein (PrP). These diseases affect both humans and animals, leading to severe neurological deterioration. Prion diseases in humans include Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal familial insomnia (FFI), and kuru. Known forms in animals include Scrapie, Bovine Spongiform Encephalopathy (BSE), Chronic Wasting Disease (CWD), Transmissible Mink Encephalopathy (TME) and Feline Spongiform Encephalopathy (FSE). One of the key factors affecting susceptibility to prion disease is genetic variation in the PRNP gene, which encodes PrP. Among the most studied polymorphisms, the M129V variant in humans plays a major role in disease susceptibility. Homozygosity for methionine (M/M) at codon 129 increases the risk of prion diseases, while heterozygosity (M/V) provides partial resistance. Similarly, in animals, specific PRNP polymorphisms such as Q171R in sheep confer resistance to scrapie, while certain genetic variants in deer affect CWD susceptibility. These polymorphisms are important for understanding disease transmission, species barriers, and potential resistance mechanisms. This review comprehensively examines prion diseases in both humans and animals, focusing on PRNP polymorphisms and their effects on disease susceptibility. Understanding these genetic variations is important for disease prevention, risk assessment, and development of potential treatment strategies.

Keywords: prion diseases, PRNP polymorphisms, transmissible spongiform encephalopathies, genetic susceptibility.

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Introduction

Transmissible Spongiform Encephalopathies (TSE), also known as prion diseases, are fatal neurodegenerative disorders that arise due to the misfolding of the prion protein and are observed to affect humans and various animal species (Whitechurch et al., 2017). Distinctive histopathological features include the formation of vacuoles within neurons, giving the tissue a spongy appearance, neuronal loss, gliosis, and prion protein aggregates of varying sizes associated with the disease (Sigurdson et al., 2018).

The discovery of the prion protein has greatly accelerated knowledge about the biology and pathogenesis of TSE diseases, as it has been found to play a critical role in disease susceptibility and the TSE species barrier, and it may also be a component of TSE (Chesebro, 2003). The species barrier is evidenced by the prolonged incubation period observed when prion proteins from one species are used to infect another species (Moore et al., 2005).

While normal cellular prion protein (PrPC) has a predominantly alpha-helical structure, misfolded prion protein (PrPSc) has a predominantly beta-sheet structure (Pan et al., 1993). PrPSc forces the normally properly folded PrPC protein found in the body to

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become misfolded, a process that is how prions replicate (Ma et al., 2022). PrPSc molecules form aggregates and become resistant to cellular digestion. It can accumulate in lymphoid and nervous tissues, especially in the central nervous system (DeArmond et al., 1985). However, different genetic backgrounds can dramatically affect the protein aggregation process and toxicity. Genetic variation plays a key role in the disease process by determining how the protein will misfold and when and how its aggregation will occur (Gidalevitz et al., 2013).

There are several key moments in the development of the current understanding of TSEs in humans. First, in 1959, veterinary pathologist W.J. Hadlow has recognized the similarities between Scrapie, a slowly progressive infection in sheep, and Kuru, a fatal neurodegenerative disease affecting only people of a single language group in the mountainous interior of New Guinea. Based on his knowledge of Scrapie, Hadlow has initiated attempts to transmit Kuru. In the same year, I. Klatzo has suggested that the histopathology of Kuru disease was similar to Creutzfeldt-Jakob disease (CJD) (Asher and Gregori, 2018). Many experiments have conducted during this period laid to laying the foundation for the concept of TSE. Considering that the infectious agent was a new virus, TSE was classified as a slow virus infection. In 1982, Prusiner examined the infectious fraction of brain homogenate infected with Scrapie, identified this agent as proteinaceous infectious particles resistant to nucleic acid-modifying treatments, and named them prions (Hizume and Mizusawa, 2007). Prusiner named this new particle 'prion' by combining the words proteinaceous and infectious. Prusiner was awarded the Nobel Prize in 1997 for this work (Gupta, 1997).

Animal prion diseases have been known since 1732, when Scrapie was described in a Merino sheep in Spain and later documented in sheep in the UK (Liberski, 2012). In the 1960s, Scrapie-like diseases, later known as Transmissible Mink Brain Disease (TMD) and Chronic Wasting Disease (CWD), were described in mink and deer in North America. However, prion diseases became more important in 1986 when the first report of a Scrapie-like disease affecting cattle was published. This new disease was named Bovine Spongiform Encephalopathy (BSE) (Wells et al., 1987). The economic importance of cattle and the interest in these pathologies increased significantly in 1996 when BSE was linked to a variant of Creutzfeldt-Jakob Disease (CJD) in humans and was therefore considered a zoonosis (Bruce et al., 1997).

First detected in the UK in 1986, BSE infected an estimated 1-3 million cattle and more than 180,000 clinical cases were confirmed before contaminated feed was banned in 1992 (Smith & Bradley, 2003). While cases declined following controls in the UK, earlier exports spread BSE to Europe. In May 2003, Canada's Alberta outbreak had a global impact when it triggered international trade restrictions and devastated the beef industry, which relied on exports for 47% of production. The embargo created sector-wide shocks in agriculture and transportation, while the US market simultaneously faced demand declines and export losses, collectively damaging farm incomes and worsening the mental health of rural communities (Rasool et al., 2023).

Prion diseases have become more important in recent decades due to the susceptibility of ruminants to prion diseases, the possibility of transmission from small ruminants to cattle, the introduction of beef for human consumption and the occurrence of zoonotic diseases. Breeding efforts have been initiated in the UK and some EU countries with the identification of PRNP polymorphisms associated with resistance/ susceptibility to Scrapie in sheep (Gallardo and Delgado, 2021).

Within species, sequence variants of PRNP may give the prospective host a different risk of succumbing to prion diseases (Stewart et al., 2012).

The aim of this review is to understand the molecular basis of prion diseases and to evaluate the relationship between genetics and resistance differences between species.

Molecular structure of prion proteins

The prion protein (PrP) represents a unique category of amyloidogenic proteins implicated in various pathological conditions. As a membrane-anchored glycoprotein, the cellular isoform (PrPC) is ubiquitously expressed across diverse eukaryotic cell types. Its remarkable evolutionary conservation and near-universal presence in mammalian species suggest fundamental biological significance, though the precise physiological roles of PrPC remain elusive (Kupfer et al., 2009).

The cellular form of the prion protein is anchored by glycosylphosphatidylinositol (GPI) and contains two glycosylation sites. The mature prion protein (PrPC) consists of a disordered N-terminal region and a C-terminal region consisting of three alpha-helices and a short beta-pleated sheet. PrPC is usually found in the outer leaflet, in lipid-rich regions of the cell membrane (Sigurdson et al., 2018).

The pathogenesis of prion diseases involves the structural conversion of the normal cellular prion protein (PrPC) into its pathogenic isoform (PrPSc). This conformational transition represents the fundamental

event in prion propagation. The biological properties of a prion strain are encoded by the sequence of the host's chromosomal PrP gene. Unlike conventional pathogens, prions lack a nucleic acid genome. Transgenic studies have demonstrated that PrPSc acts as a template, facilitating the refolding of newly synthesized PrPC molecules into the PrPSc conformation through a process mediated by auxiliary protein factors (Prusiner, 1998).

The exact structure of PrPSc is still not fully understood because u nlike viruses or bacteria, prions do not contain genetic material; they are simply misfolded proteins. This unusual structure means that standard laboratory tools do not work well for studying them. The infectious prion (PrPSc) looks almost identical to the normal version found in healthy brains (PrPC). Our immune system cannot tell them apart, and we cannot produce antibodies that target only the bad ones. Experimental limitations further constrain research: prions require biosafety level 3 containment, replicate sluggishly in vitro (often requiring months to years in animal models), and lack standardized reagents. Compounding these scientific hurdles are systemic issues - scarce specialized facilities, minimal funding opportunities, and consequently, a shrinking research workforce. These collective barriers slows discovery and therapeutic development for prion diseases (Erdtmann and Sivitz, 2003).

In addition, the existence of different prion strains makes determining this structure more complicated. Elucidating the structure of PrPSc can help us understand how prions replicate and the molecular basis of different strains. This knowledge will also play an important role in the development of new treatments for prion diseases (Zhu and Aguzzi, 2021).

Prion protein in spongiform diseases of humans

Creutzfeldt-Jakob disease (CJD): CJD is the most common human prion disease worldwide. It can be classified as sporadic, acquired or familial (Iwasaki, 2016). CJD is a contagious, subacute and fatal neurodegenerative disease characterized by spongiform transformation of the brain. Despite its rarity, it has attracted the attention of scientists due to its distinct clinical features and novel transmission mechanism since Pruisner described the pathogenic process in 1982. In the late 1990s, the emergence of a new variant seen in cattle increased the interest in this disease and led to more stringent measures to ensure the safety of cattle feed and food products (Narayan and Dutta, 2005).

It is classified as sporadic, hereditary, or acquired (Will, 2003). The most common form worldwide is the sporadic form (sCJD). The disease begins with rapidly progressive dementia, cerebellar ataxia, visual disturbances, and myoclonus, and eventually patients develop akinetic mutism. In most countries, the average lifespan of this disease is only four months, and it is very rare for patients to survive more than two years (Sikorska et al., 2012). Genetic Creutzfeldt-Jakob Disease (gCJD) is often indistinguishable from sCJD. This disease is caused by various mutations in the PRNP gene. To make a definitive diagnosis, a first-degree relative of the patient must have been diagnosed with CJD or a disease-specific mutation must be detected in the PRNP gene. In this way, it can be confirmed that the disease is a genetic form (Baldwin and Correll, 2019). Acquired prion protein diseases can be categorized as Variant Creutzfeldt-Jakob Disease (vJCD), Iatrogenic Creutzfeldt-Jakob Disease (iJCD) and Kuru (Tee et al., 2018). Variant CJD (vCJD) was first described in the United Kingdom in 1996. It is a zoonotic human prion disease resulting from contamination of human food with material obtained from cattle infected with BSE. It has important epidemiological, clinical and neuropathological differences from other types of human prion disease. The link between BSE and vCJD has been supported by a variety of biological evidence (Brandel and Knight, 2018). The first evidence of iatrogenic transmission of Creutzfeldt-Jakob disease (CJD) occurred with a corneal transplant in 1974. Since then, other routes of transmission have been discovered, including neurosurgical instruments, deep electrodes, pituitary hormones from human cadavers, and dura mater grafts (Will, 2003).

Kuru: Kuru was first reported by Gajdusek and Vincent Zigas in 1957. It means "tremor" in the Fore language of Papua New Guinea and has been identified as resulting from cannibalism. The disease is characterized by tremors, involuntary movements, and a cerebellar ataxia that eventually results in death. Neuropathologically, kuru is recognized by the presence of amyloid "kuru" plaques in the brain (Liberski et al., 2012).

Gerstmann-Straussler-Scheinker syndrome (GSS): GSS is an inherited prion disease clinically characterized by early onset of progressive cerebellar ataxia. It is the first type of TSE in which a mutation in the prion protein gene was discovered. (Zhao et al., 2019). The disease is widespread, with multicentric PrP-amyloid plaques in the brain. Symptoms usually begin in the 40s and last an average of four years (Pérez-Carbonell et al., 2023).

Fatal familial insomnia (FFI): FFI is a rare and fatal inherited prion disease. It is inherited as an autosomal dominant trait and is caused by a mutation in the PRNP

gene (Khan et al., 2024). The major clinical features of FFI include progressive and severe insomnia, waking "sleep," hallucinations, autonomic disturbances indicative of sympathetic overdrive, increased circulating catecholamine levels, cognitive changes, ataxia, and endocrine manifestations. Later cognitive changes include a state of confusion resembling dementia and end in death (Schenkein and Montagna, 2006).

Prion protein in transmissible spongiform diseases of animals

Scrapie: Scrapie disease was the first prion disease identified in sheep and recognized as early as 1732. It was also detected in goats in 1942. There are two main forms of scrapie: Classic scrapie and atypical scrapie (Goldmann, 2018).

Signs of scrapie in sheep begin with mild social behavioural disorders, followed by loss of balance, tremors, severe itching and wool loss. Animals may rub against fences or bite themselves to relieve the itching sensation. These symptoms may last from 2 weeks to 6 months. In some cases, sheep may die without showing any symptoms (Hunter, 1998).

Bovine Spongiform Encephalopathy (BSE): BSE was first scientifically reported in 1987, but the first case was confirmed in 1986 and the first clinical case probably occurred in 1985. Meat and bone meal was identified as the source of transmission of the disease as a result of detailed epidemiological studies conducted in 1987. BSE was not recognized as a zoonotic disease for a long time. However, in 1996, it was revealed that BSE was associated with a new human prion disease, variant Creutzfeldt-Jakob disease (vCJD), and this led to an unprecedented public health crisis in Europe. (Houston and Andréoletti, 2019).

Postural and movement disorders are observed in BSE disease and usually manifest as hind leg ataxia, tremors and falls. Sensory changes and most notably hyperesthesia occur. In the majority of cases, nervous system symptoms are observed, indicating a central nervous system disorder (Kimberlin, 1992).

Chronic wasting disease (CWD): CWD was first observed in captive deer facilities in the US state of Colorado in 1967 and was classified as a TSE in 1979. In 1981, it was also discovered in wild deer populations. The disease is highly contagious and can have a prevalence of 40-50% in wild deer populations and 80-100% in captive populations. These high rates of transmission have made controlling CWD a priority for wildlife managers and conservationists, especially for economically and conservationally important species. (Winter and Escobar, 2020).

Transmissible mink encephalopathy (TME): TME was first described in 1947 on two mink farms in Wisconsin and Minnesota. All adult animals on the Wisconsin farm developed a progressive neurological disease that resulted in incoordination of movement, lethargy, weakness, and death. A similar disease occurred on a Minnesota farm during the same period. The last case of TME was reported in Stetsonville, Wisconsin, in 1985. A rare condition known as TME has been linked to farm-raised mink being exposed to an undisclosed feed contaminant (Marsh and Hadlow, 1992).

Feline spongiform encephalopathy (FSE): FSE was first reported in 1990 by Wyatt et al. in a Siamese cat in England. The cat developed a progressive neurological disease with front and hind limb ataxia. The symptoms worsened over a period of six weeks. The animal was euthanized because it did not respond to treatment. Microscopic examination after autopsy revealed neuronal vacuolization, neuropil spongiosis and astrocytosis in the gray matter of the brain. These findings are signs of scrapie-like spongiform encephalopathy (Kim et al., 2021).

It is believed that cats consuming contaminated feed are the most likely cause of the illness. The ban on SBO (specified bovine offal) introduced in 1990 was an important step in protecting cats from exposure to BSE (Bradley, 2002).

PRNP gene polymorphisms and genetic susceptibility human

In humans, polymorphisms at codon 129 of the PRNP gene significantly influence susceptibility to sporadic Creutzfeldt-Jakob disease (sCJD). This codon can exhibit three genotypic variants: methionine-methionine (MM), methionine-valine (MV), and valine-valine (VV) (Appleby et al., 2022). Meta-analytic evidence indicates that methionine homozygosity (MM) confers a substantially higher risk of developing sCJD compared to heterozygosity (MV) (Kim and Jeong, 2021).

Polymorphisms at codon 129 do not alter the native conformation of cellular PrP and do not affect copper (II) ion binding. In addition, they have no measurable effect on the efficiency of conversion to the β-sheet-rich PrP conformation. However, under partially denaturing conditions, the polymorphism significantly modulates the ability of the protein to spontaneously form amyloid fibrils. These findings suggest that although residue 129 does not affect the physiological properties of PrP^{o}, it plays a critical role in pathological aggregation (Lewis et al., 2006).

Beyond disease susceptibility, codon 129 polymorphisms also modulate clinical phenotypes. Notably, MV heterozygotes exhibit the longest median survival time following disease onset, whereas VV and MM homozygotes demonstrate progressively shorter

survival durations (Llorens et al., 2020).

The E219K polymorphism in the PRNP gene, which results in a glutamate-to-lysine substitution at codon 219, has been identified as a potential protective factor against sCJD (Kobayashi et al., 2015). Although this genetic variant is common in Asian populations, it is rarely found in sCJD patients, suggesting that it may help prevent the disease.

To investigate this protective effect, researchers created mice carrying the human E219K variant and exposed them to both variant CJD (vCJD) and sCJD prions. Surprisingly, the results showed that the 219K prion protein was converted to the disease-associated form (PrPSc) more efficiently than the normal 219E version. However, when mice carried both variants (E/K heterozygotes), they showed significantly lower levels of prion conversion compared to mice with only E/E or K/K homozygotes. This phenomenon, called heterozygous inhibition, suggests that the protective effect of E219K is not due to completely blocking prion formation, but rather to disrupting the misfolding process when both variants are present. Essentially, having two different versions of the prion protein provides a natural defense mechanism against sCJD by interfering with the chain reaction required for the disease to spread (Hizume et al., 2008). This polymorphism alters protein function through different molecular mechanisms. This glutamate-to-lysine substitution at residue 219 creates a positive charge in the C-terminal domain, disrupting native electrostatic interactions and reducing structural stability. Biochemical studies suggest that E219K enhances β-sheet formation and promotes amyloidogenic transformation, particularly under destabilizing conditions. The mutation appears to facilitate aberrant protein-protein interactions, potentially increasing the aggregation propensity and neurotoxicity of PrP. In contrast to the M129V polymorphism, which primarily affects disease susceptibility and strain specificity, E219K directly alters the biophysical properties of PrP, including its interaction with metal ions and other pathogenic proteins such as amyloid-β (Wang et al., 2024)

In addition, the codon 129 polymorphism (MM, MV, VV) of the PRNP gene significantly affects the progression of kuru. While all three genotypes can develop kuru, MV heterozygotes show specific resistance by significantly longer incubation periods (Mead et al., 2019). And a remarkable genetic adaptation has been identified in the Eastern Highlands of Papua New Guinea, where the G127V polymorphism in the PRNP gene confers complete resistance to kuru (Mead et al., 2009). The G127V polymorphism in the prion protein (PrP) protects against prion diseases through structural and kinetic mechanisms. The replacement of glycine with valine at position 127 creates a bulkier side chain in the critical β2-α2 loop region. This restricts the flexibility of the loop, preventing conformational changes required for pathogenic transformation to PrP^Sc. The mutation both destabilizes disease-prone intermediates and disrupts molecular interactions required for prion propagation. Unlike other protective polymorphisms that affect charge or metal binding, G127V acts primarily through physical inhibition of the transformation process (Zheng et al., 2018). This variant represents a striking example of human evolution. Its high frequency in affected populations suggests a strong selection pressure during the kuru epidemic and how infectious diseases can shape human genetics.

Sheep and Goat

Sheep exhibit natural genetic variations in the PRNP gene that significantly influence their susceptibility to scrapie, a fatal neurodegenerative disease. Research has identified three key codons (136, 154, and 171) that play pivotal roles in disease resistance mechanisms.

The presence of valine (V136), arginine (R154), and glutamine (Q171) at these respective codons confers increased susceptibility, particularly when occurring together as the V136R154Q171 haplotype. In contrast, two genetic variants demonstrate protective effects: the ARR haplotype, characterized by alanine at codon 136 (A136) and arginine at codon 171 (R171), and the presence of lysine at codon 171 (K171).

Notably, codons 136 and 171 exert stronger influence on scrapie susceptibility than codon 154. Genotype analysis reveals a clear resistance hierarchy: ARR/ARR genotypes show the highest resistance to classical scrapie, followed sequentially by ARR/ARQ, ARQ/ARQ, ARR/VRQ, ARQ/VRQ, and VRQ/VRQ genotypes, with the latter being most susceptible (Cassmann & Greenlee, 2020).

These polymorphisms affect scrapie susceptibility through conformational control of the protein's β-folding tendency. The protective VRQ/ARR haplotype (Val136-Arg154-Arg171) stabilizes the α-helical structure of cellular PrP via enhanced salt bridges between Arg154-Arg171 and the C-terminal domain, whereas disease-associated variants (e.g. ARQ) exhibit greater conformational flexibility that facilitates β-sheet conversion. The arginine residues of the ARR allele provide a kinetic barrier to both electrostatic repulsion of PrP^Sc templates and misfolding in the β2-α2 loop region, explaining the almost complete resistance of ARR/ARR sheep to classical scrapie (Bossers et al., 1997; Jacobs et al., 2011)

Goats share the same A136, R154H, and Q171 alleles as sheep, but the A136 and Q171 alleles are not polymorphic. As in sheep, the H154 allele has been associated with low risk for Classical Scrapie but high risk for Atypical Scrapie. Other alleles associated with Scrapie resistance include H143R, N146S/D, R211Q, and Q222K (Lacroux et al., 2014).

Cattle

Extensive research on bovine spongiform encephalopathy (BSE) has revealed notable differences from scrapie in terms of genetic susceptibility. Unlike small ruminants where PRNP polymorphisms strongly influence disease susceptibility, cattle show no clear association between BSE infection and prion protein (PrP) polymorphisms (Mead et al, 2019). However, genetic studies have identified a 12-base pair deletion in the PRNP gene that appears to modulate BSE risk, with both homozygous and heterozygous states demonstrating increased susceptibility (Haase et al., 2007; Sander et al., 2004).

Studies suggest that this deletion reduces PRNP expression levels by eliminating a Sp1 transcription factor binding site. While German and British studies have linked indel polymorphisms with BSE, this association was not statistically significant in Japanese Holsteins, suggesting that breed-specific genetic backgrounds may influence disease modulation (Gurgul and Slota, 2007).

A significant breakthrough occurred in 2006 with the identification of an atypical BSE case in Alabama, USA. This case revealed a polymorphic variation at codon 211 of the PRNP gene, involving a glutamate-to-lysine substitution (E211K). This mutation holds particular interest as it represents a molecular parallel to the pathogenic E200K mutation in humans, which is known to cause familial Creutzfeldt-Jakob disease (Heaton et al., 2008). The origin of this polymorphism remains uncertain, with current research unable to determine whether it represents an inherited trait or spontaneous mutation (Nicholson et al., 2008).

The E211K mutation causes a small but important change in the prion protein, possibly making it more likely to misfold. Though the general structure remains similar to the wild-type, this mutation reduces stability and may influence how the protein refolds, which could contribute to disease development, as seen in similar human mutations (Nicholson et al.,2008; Hwang and Nicholson, 2018)

Deer

Research on chronic wasting disease (CWD) in North American deer species has revealed significant amino acid variations in the prion protein that influence disease susceptibility. White-tailed deer (Odocoileus virginianus) exhibit a notable polymorphism at codon 96, where the typical glycine (96G) is substituted by serine (96S). A parallel variation occurs in mule deer (O. hemionus) at codon 225, with phenylalanine (225F) replacing the more common serine (225S).

Epidemiological studies demonstrate that these polymorphisms affect CWD prevalence in wild populations. Heterozygous white-tailed deer (96GS) and heterozygous mule deer (225SF) show reduced CWD incidence compared to their homozygous wild-type counterparts. Notably, deer homozygous for either variant (96SS or 225FF) exhibit the lowest disease occurrence, though complete resistance has not been observed (Johnson, 2006; Jewell, 2005).

At codons 95 and 96 in the unstructured N-terminal domain, H95Q and G96S substitutions destabilize the initial folding dynamics of PrPC, disrupting CWD propagation. However, polymorphisms at codons 225 and 226 show more profound effects. The S225F substitution stabilizes a critical tertiary epitope between the β2-α2 ring and α-helix 3 via a novel hydrogen bond (Y228-D170), paradoxically conferring resistance to CWD while prolonging SSBP/1 incubation. The Q226E variant significantly inhibits prion propagation, possibly by disrupting electrostatic interactions required for interspecies conformational templating (Angers et al., 2014).

These amino acid substitutions appear to modify disease progression rather than prevent infection. Both polymorphisms significantly extend the incubation period and decelerate clinical disease development (Johnson, 2006; Jewell, 2005).

Dog

Canines represent a unique case among mammalian species, as they have never been documented to develop prion diseases despite potential exposure to infectious agents like BSE. This remarkable resistance prompted extensive investigation into the genetic basis of canine protection against prion pathogenesis.

A critical discovery emerged from analysis of the canine PRNP gene, revealing a distinctive aspartic acid residue (Asp163) at position 163. This negatively charged amino acid appears to confer structural stability to the prion protein, preventing the conformational changes necessary for disease propagation. Experimental validation using transgenic mouse models expressing canine PrP demonstrated complete resistance - even when challenged with diverse prion strains, these mice showed neither clinical signs nor detectable protein misfolding in brain tissue or in vitro amplification assays (Vidal et al., 2020).

Further computational studies have elucidated additional molecular details of this resistance mechanism. Comparative analysis of PrP structural

dynamics revealed that canine variants containing Glu182 or Gly182 alleles form fewer hydrogen bonds than those with Asp182 alleles (Kim et al., 2020). This reduction in stabilizing interactions may contribute to the observed resistance by altering the energy landscape of protein misfolding.

These findings collectively suggest that canine prion resistance results from multiple protective features in their PrP sequence, with Asp163 playing a particularly crucial role. The absence of prion disease in dogs, despite evolutionary exposure to scrapie and BSE agents, highlights the effectiveness of these molecular adaptations.

Cat

The genetic basis of feline spongiform encephalopathy (FSE) susceptibility remains poorly characterized compared to other mammalian species. Limited investigations into domestic cat (Felis catus) PRNP gene polymorphisms have failed to identify disease-associated variants that clearly modulate FSE risk, unlike the well-documented resistance and susceptibility alleles found in ruminants and other species (Kim et al., 2021).

However, the feline prion protein exhibits unique structural variations in the N-terminal domain that distinguish it from other carnivores. Although most feline species have five nonapeptide repeats (P(Q/H) GGG(G/-)WGQ) in the PrP N-terminal region, significant intra- and interspecies variation exists. Notably, mountain lions (Puma concolor) display a four-repeat variant, and domestic cats (Felis catus) exhibit both four- and five-repeat polymorphisms. Interestingly, Asian lions (Panthera leo persica) retain five repeats, whereas their African counterparts (Panthera leo) have four repeats, potentially representing genetic differentiation at the subspecies level. A distinctive felid -specific feature is the presence of alanine-containing repeats that are notably absent in phylogenetically related families such as Viverridae (e.g. binturongs) and Hyaenidae (e.g. spotted hyenas). These structural differences in the octapeptide repeat region suggest that feline PrP has undergone unique evolutionary adaptations that may affect metal-binding properties, protein folding dynamics, and potential susceptibility to prion diseases (Stewart et al., 2012).

Other Species

There have been no reports of naturally occurring TSE in rabbits, horses, pigs, or dogs. However, studies with experimental infections have reduced the number of TSE-resistant strains. For example, experimental transmission of BSE to pigs via intracerebral and intraperitoneal injections has been reported (Konold et al., 2009). Experimental transmission of various prion strains has also been conducted in rabbits (Vidal et al., 2013).

Conclusion

Prion diseases are zoonotic disorders affecting a wide range of mammalian species, including humans. Spongiform encephalopathies, which are of major concern in cattle, sheep, and goat production, have also been observed in wildlife and have led to significant epidemics in the past.

Although considerable progress has been made in identifying the pathological features and transmission routes of prion diseases, the precise molecular mechanisms governing susceptibility, resistance, and misfolding remain incompletely understood. Therefore, further research should focus on the structural and genetic determinants of prion protein misfolding, host-specific factors influencing disease progression, and the identification of potential molecular markers for early diagnosis.

In addition, advances in recombinant protein studies, transgenic animal models, and high-throughput screening techniques hold promise for the development of effective therapeutic strategies and preventive interventions. A deeper understanding of these mechanisms could not only contribute to controlling prion diseases in livestock but may also provide critical insights applicable to other neurodegenerative disorders such as Alzheimer's and Parkinson's disease.

More research and a better understanding of the mechanisms behind susceptibility and resistance are required to prevent prion illnesses and create novel treatment approaches.

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