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韓国でツツガムシ病患者急増

このところ、ツツガムシ病の患者が急増している。20日、疾病管理本部の発表によると、2002年に1919人だったツツガムシ病の患者数が、04年は4698人、06年には6420人に増加したことが分かった。1993年末にツツガムシ病が法定伝染病に指定されて以来、患者数は実に25倍以上増加した。

ツツガムシ病は、主に9月以降、ツツガムシ菌に感染したツツガムシ(ダニの一種)の幼虫に刺されることにより感染する。10日間程度の潜伏期を経ると、突然高熱が発生し、目の充血、頭痛、筋肉痛、発疹などの症状が現れる。また、刺口がただれ、黒いかさぶたとなる場合もある。ツツガムシという名前は、ダニを意味する日本語(恙虫)に由来する。

サムスンソウル病院感染内科の白敬薗(ペク・ギョンラン)教授は、「抗生物質で比較的容易に治療できるが、初期症状が風邪と似ているため、適切な治療を受けずにそのまま放置すると、心不全や肺炎で死亡する危険性もある。秋にひどい風邪の症状が現れ、虫に刺された所があったり発疹が出たりした場合には、直ちに病院で治療を受けたほうがよい」と話した。

疾病管理本部伝染病監視チームのパク・ヘギョン研究員は、ツツガムシ病患者が増加したことに対し、「最近、伝染病管理が強化され、患者が確実に報告されるようになった上、温暖化によりダニの活動期間が長くなったためと思われる」と話した。ツツガムシ病は、主に野山で畑仕事をする農夫や、農村に住む人たちが感染することが多かったが、最近では登山などアウトドア活動が活発になったことを受け、一般の患者も増えている。

ツツガムシ病を予防するには、ダニに刺されないよう長袖の服を着たり、靴下を履くなど皮膚の露出を最大限抑えなければならない。また秋に入り野外に出る際は、草地に直接座ったり、草むらで用を足したりすることは控えなければならない。

・智[illegible]・ジヘ)記者

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研究報告の概要

本総説ではヒトプリオン病に関する最新の知見として，弧発性，家族性あるいは変異型クロイツフェルト・ヤコブ病（vCJD）（ウシの BSE を発症させるものと同じプリオン株によってヒトに発症する）のように後天性であるかどうかについて要約している。これらの複合的な神経変性障害の根底にある分子メカニズムは，宿主にコードされたプリオン蛋白（PrP^{c}）が異常アイソフォーム（PrP^{Sc}）へと変換するためであると考えられている。PrP^{Sc} は正常プリオン蛋白と比較すると，蛋白分解酵素感受性及び界面活性剤可溶性の変化を示す。PrP^{Sc} は伝播性プリオンの主要な，且つ，恐らく唯一の成分（蛋白単独モデル）であると考えられている。ヒト PrP 129 番目の遺伝子多型（メチオニン又はバリンをコードしている）はプリオン病の感受性に大きく影響を及ぼし，メチオニンホモ接合体は弧発性及び後天性クロイツフェルト・ヤコブ病（CJD）に罹患しやすいことがわかっている。興味深いことに，ヘテロ接合体の個体は，パプアニューギニアにおけるクールー病の最高齢の生存者であることが確認されている〔クールー病は食人の慣習（カニバリズム）により伝播された後天性プリオン病である〕。さらに，これまでに調査した vCJD の臨床症例はいずれもメチオニン 129 ホモ接合体であった。PrP の 129 残基は，PrP^{Sc} 又はその前駆体の立体構造，あるいはその形成における動態に影響を及ぼす可能性が高い。

弧発性 CJD とは対照的に，vCJD は若年患者に発現し，罹患期間が長い。双方とも同様の神経病理学的特性（海綿状変性，神経細胞の脱落及び星状細胞増加症）が認められるが，ほとんどの PrP アミロイド斑は vCJD で認められる。ヒトプリオン病でみられる臨床病理学的な不均質性は，様々な物理化学的特性を持つ独特の PrP^{Sc} アイソフォームに変換させる特異的プリオン株によって生じると考えられる。本総説には，現在までに確認された 4 種の主要な PrP^{Sc} の型が記載されている。1～3 型は典型的な CJD で認められる一方，4 型は唯一 vCJD で認められ，異なるグリコシル化プロファイルならびに蛋白分解酵素消化後の特異的なパターンを示す。さらに，PrP^{Sc} の異常アイソフォームの伝播は宿主ゲノムによって影響を受けていると考えられ，プリオン接種源もまた疾患の表現型に影響を及ぼしている可能性がある。家族性及び弧発性 CJD とは対照的に，vCJD ではリンパ細網組織内で PrP^{Sc} が容易に検出される。vCJD の脳で認められる 4 型の PrP^{Sc} とは異なる，特異的な型である 4t 型は vCJD 患者の扁桃腺で確認されている。リンパ細網組織には神経侵襲前に感染するため，扁桃生検により明確かつ早期の vCJD 診断が可能である。

依然として不明な点が多く，クールー病が 40～50 年にわたる長い潜伏期を伴うことを考慮すると，ヒト vCJD の伝播性の程度を確実に予測することはできない。そのため，vCJD プリオンの二次的（ヒト間の）伝播を回避するための最大限の注意が必要である。

使用上の注意記載状況・その他参考事項等

BYL-2007-0283

報告企業の意見	今後の対応
この総説は，ヒトプリオン病の知見とその複雑な疾患の重要点を要約している。現時点で，多くの不明点が残っているが，ヒト間での vCJD 感染を予防する為には，あらゆる予防策を講じることが賢明であると考える。	プリオン病の伝播リスクについて，引き続き情報収集に努める。

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Review

Update on human prion disease

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Abstract

The recognition that variant Creutzfeldt–Jakob disease (vCJD) is caused by the same prion strain as bovine spongiform encephalopathy in cattle has dramatically highlighted the need for a precise understanding of the molecular biology of human prion diseases. Detailed clinical, pathological and molecular data from a large number of human prion disease patients indicate that phenotypic diversity in human prion disease relates in part to the propagation of disease-related PrP isoforms with distinct physicochemical properties. Incubation periods of prion infection in humans can exceed 50 years and therefore it will be some years before the extent of any human vCJD epidemic can be predicted with confidence.

Keywords: Bovine spongiform encephalopathy; Creutzfeldt-Jakob disease; Fatal familial insomnia; Gerstmann-Sträussler-Scheinker disease; Kuru; Prion; Prion disease; Prion protein; Transmissible spongiform encephalopathy; Variant Creutzfeldt-Jakob disease

1. Introduction

Prion diseases are fatal neurodegenerative disorders that include Creutzfeldt–Jakob disease (CJD), Gerstmann–Sträussler–Scheinker disease (GSS), fatal familial insomnia (FFI), kuru and variant CJD (vCJD) in humans [1,2]. Their central feature is the post-translational conversion of host-encoded, cellular prion protein (PrP^C), to an abnormal isoform, designated PrP^{Sc} [1,2]. This transition appears to involve only conformational change rather than covalent modification and confers PrP^{Sc} with partial resistance to proteolytic degradation and detergent insolubility. Human prion diseases are biologically unique in that the disease process can be triggered through inherited germline mutations in the human prion protein gene (*PRNP*), infection (by inoculation, or in some cases by dietary exposure) with prion-infected tissue or by rare sporadic events that generate PrP^{Sc} [2–4]. Substantial evidence indicates that an abnormal PrP isoform is the principal, if not the sole, component of the transmissible infectious agent, or prion [1,2,5,6]. The mechanism of neurodegeneration that accompanies the accumulation of PrP^{Sc} in the brain remains unknown [7] although there is increasing evidence that this may involve an apoptotic mechanism involving inhibition of the proteosome [8]. The existence of multiple strains or isolates of prions has been difficult to accommodate within a protein-only model of prion propagation and understanding how a protein-only infectious agent can encode distinct disease phenotypes in humans has been of considerable biological interest. A wealth of experimental evidence now suggests that prion strain diversity is encoded within PrP itself and phenotypic diversity in human prion diseases relates to differing physicochemical properties of abnormal PrP isoforms [9–18].

2. Aetiology and clinical features of human prion diseases

Human prion diseases can be divided aetiologically into inherited, sporadic and acquired forms [1,2]. Human prion diseases with distinct aetiologies are associated with a range of clinical presentations which are now seen as clinico-pathological syndromes rather than individual disease entities [3,4,19].

3. Sporadic CJD

Approximately 85% of cases of human prion disease occur sporadically as Creutzfeldt–Jakob disease (sporadic CJD) at a

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rate of 1–2 cases per million population per year across the world, with an equal incidence in men and women [20,21]. The aetiology of sporadic CJD is unknown, although hypotheses include somatic *PRNP* mutation [20,22,23], or the spontaneous conversion of PrP^{C} into PrP^{Sc} as a rare stochastic event [22]. Polymorphism at residue 129 of human PrP (encoding either methionine (M) or valine (V)) powerfully affects susceptibility to human prion diseases [21,24–28]. About 38% of Europeans are homozygous for the more frequent methionine allele, 51% are heterozygous, and 11% homozygous for valine. Homozygosity at *PRNP* codon 129 predisposes to the development of sporadic and acquired CJD [21,24–28]. Most sporadic CJD occurs in individuals homozygous for this polymorphism. This susceptibility factor is also relevant in the acquired forms of CJD, most strikingly in vCJD; all clinical cases studied so far have been homozygous for codon 129 methionine of *PRNP* (see below). Additionally, a *PRNP* susceptibility haplotype has been identified indicating additional genetic susceptibility to sporadic CJD at or near to the *PRNP* locus [29,30].

Classical sporadic CJD presents as a rapidly progressive multifocal dementia usually with myoclonus. The onset is usually in the 45–75 years age group with median age at death of 68 years [21]. The clinical progression is typically over weeks progressing to akinetic mutism with a median disease duration of 5 months [21]. Prodromal features, present in around a third of cases, include fatigue, insomnia, depression, weight loss, headaches, general malaise and ill-defined pain sensations. In addition to mental deterioration and myoclonus, frequent additional neurological features include extrapyramidal signs, cerebellar ataxia, pyramidal signs and cortical blindness. Raised cerebrospinal fluid 14-3-3 protein, neuronal specific enolase (NSE), and S-100, although not specific for CJD, may be helpful diagnostically in the appropriate clinical context [21,31–36]. The electroencephalogram (EEG) may show characteristic pseudoperiodic sharp wave activity that is helpful in diagnosis but present only in around 60% of cases [21]. In contrast cortical signal changes on diffusion weighted MRI are extremely helpful in the diagnosis of CJD [37–42]. Neuropathological confirmation of CJD is by demonstration of spongiform change, neuronal loss and astrocytosis. PrP amyloid plaques are usually not present in CJD [43] although PrP immunohistochemistry, is nearly always positive [43–45].

Atypical forms of sporadic CJD are well recognised. 10% of cases of CJD have a much more prolonged clinical course with a disease duration of over 2 years [46]. Around 10% of CJD cases present with cerebellar ataxia rather than cognitive impairment, so-called ataxic CJD [47]. Heidenhain's variant of CJD refers to cases in which cortical blindness predominates with severe involvement of the occipital lobes. The panencephalopathic type of CJD refers to cases with extensive degeneration of the cerebral white matter in addition to spongiform vacuolation of the gray matter and has been predominately reported from Japan [47–49]. Amyotrophic variants of CJD have been described with prominent early muscle wasting. However, most cases of dementia with amyotrophy are not experimentally transmissible and their relationship with CJD is unclear [50,51].

4. Inherited prion disease

Approximately 15% of human prion diseases are associated with autosomal dominant pathogenic mutations in *PRNP* [14,22,52–54]. How pathogenic mutations in *PRNP* cause prion disease has yet to be resolved, however, in most cases the mutation is thought to lead to an increased tendency of PrP^{C} to form PrP^{Sc}, although there is evidence to suggest that this may not be solely attributable to decreased thermodynamic stability of mutated PrP^{C} [55,56]. Experimentally manipulated mutations of the prion gene can lead to spontaneous neurodegeneration without the formation of detectable protease resistant PrP [57,58]. These findings raise the question of whether all inherited forms of human prion disease invoke disease through the same mechanism, and in this regard it is currently unknown whether all are transmissible by inoculation [52].

Over 30 autosomal dominant pathogenic *PRNP* mutations have been described [2,3,53,54]. In the appropriate clinical setting identification of a pathogenic *PRNP* mutation provides diagnosis of inherited prion disease and sub-classification according to mutation; *PRNP* analysis is also used for pre-symptomatic genetic testing in affected families [4,52,54,59]. Traditionally, inherited prion diseases have been classified by the presenting clinical syndrome, falling into three main subdivisions of either GSS, CJD or FFI. GSS classically presents as a chronic cerebellar ataxia with pyramidal features with dementia occurring much later in a clinical course that is typically longer than that seen in classical CJD [52]. Fatal familial insomnia (FFI) is characterised by progressive untreatable insomnia, dysautonmoia and dementia, selective thalamic degeneration and is most commonly associated with a missense mutation at codon 178 of *PRNP* [60], although sporadic FFI with no causative mutation in *PRNP* has been reported [61,62]. Remarkably, some families show extensive phenotypic variability which can encompass both CJD- and GSS-like cases as well as other cases which do not conform to either CJD or GSS phenotypes [19,53,54,63–66]. Progressive dementia, cerebellar ataxia, pyramidal signs, chorea, myoclonus, extrapyramidal features, pseudobulbar signs, seizures and amyotrophic features can be seen in variable combinations. Such atypical prion diseases may lack the classical histological features of a spongiform encephalopathy entirely although PrP immunohistochemistry is usually positive [64]. The existence of phenotypic overlap between individuals with different mutations and even in family members with the same *PRNP* mutation indicates that accurate classification of inherited human prion diseases should be based upon mutation alone [19,67]. Because of the extensive phenotypic variability seen in inherited prion disease and its ability to mimic other neurodegenerative conditions, notably Alzheimer's disease, *PRNP* analysis should be considered in all patients with undiagnosed dementing and ataxic disorders [19,63,64,68].

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5. Acquired prion disease

Although the human prion diseases are transmissible diseases, acquired forms have, until recently, been confined to rare and unusual situations.

5.1. Iatrogenic CJD

The two most frequent causes of iatrogenic CJD occurring through medical procedures have arisen as a result of implantation of dura mater grafts and treatment with growth hormone derived from the pituitary glands of human cadavers [69,70]. Less frequent incidences of human prion disease have resulted from iatrogenic transmission of CJD during corneal transplantation, contaminated electroencephalographic (EEG) electrode implantation and surgical operations using contaminated instruments or apparatus [69,70]. The clinical presentation in iatrogenic forms of human prion disease appear to be related to their aetiology and in particular the route of exposure to human prions [52,70,71]. Peripheral routes of infection are typically associated with longer incubation periods and usually present with a kuru-like syndrome in which ataxia rather than dementia is the prominent early clinical feature. In contrast, patients with dura mater graft-related exposure to human prions, in which infectivity is placed in closed proximity to the brain, typically have a clinical presentation similar to that of sporadic CJD [72], although exceptions with unusual clinical features have been reported [73].

5.2. Kuru

The most well-known example of acquired prion disease in humans is kuru, transmitted by cannibalism among the Fore linguistic group of the Eastern Highlands in Papua New Guinea [28,52,74,75]. The central clinical feature of kuru is progressive cerebellar ataxia and in sharp contrast to sporadic CJD, dementia is late and may be absent. A prodrome and three clinical stages consisting of an ambulatory stage, a sedentary stage and a tertiary stage have been described [52,74,75]. Remarkably, kuru demonstrates that incubation periods of infection with human prions can exceed 50 years [75]. *PRNP* codon 129 genotype has shown a pronounced effect on kuru incubation periods and susceptibility, and most elderly survivors of the kuru epidemic are heterozygotes [27,28,75]. The clear survival advantage for codon 129 heterozygotes provides a powerful basis for selection pressure in the Fore [28,75]. However, an analysis of worldwide haplotype diversity and allele frequency of coding and non-coding polymorphisms of *PRNP* suggests that balancing selection at this locus (in which there is more variation than expected because of heterozygote advantage) is much older and more geographically widespread [28]. Evidence for balancing selection has been shown in only a few human genes. With biochemical and physical evidence of cannibalism on five continents, one explanation is that cannibalism resulted in prion disease epidemics in human prehistory, thus imposing balancing selection on *PRNP* [28].

5.3. Variant CJD

The appearance of a novel human prion disease, variant CJD (vCJD), in the United Kingdom from 1995 onwards [76], and the experimental confirmation that this is caused by the same prion strain as that causing BSE in cattle [10,77–79], has led to widespread concern that exposure to the epidemic of BSE poses a distinct and conceivably a severe threat to public health in the United Kingdom and other countries [4,80]. The extremely prolonged and variable incubation periods seen with prion diseases when crossing a species barrier means that it will be some years before the parameters of any human epidemic can be predicted with confidence [75,80–83]. In the meantime, we are faced with the possibility that significant numbers in the population may be incubating this disease and that they might pass it on to others via blood transfusion, blood products, tissue and organ transplantation and other iatrogenic routes [80,84–87].

To date, the clinical presentation of human BSE infection has only been recognised as vCJD in *PRNP* codon 129 methionine homozygotes. The neuropathological features of vCJD are somewhat different from those seen in classical (sporadic or iatrogenic) CJD, and are characterised by the presence of abundant florid PrP plaques [76,88] and the propagation of type 4 PrP^{Sc} in brain [10,15] (Fig. 1). The early clinical presentation of vCJD resembles kuru more than classical CJD and consists of behavioral and psychiatric disturbances, peripheral sensory disturbance and cerebellar ataxia. Common early psychiatric features include depression, withdrawal, anxiety, insomnia, and apathy. Neurological symptoms have preceded psychiatric symptoms in a minority of cases. No common early neurological features have been reported, but paraesthesiae and/or pain in the limbs is seen in around half of the cases. However a significant proportion of patients exhibited neurological symptoms within 4 months of clinical onset, and these included poor memory, pain, sensory symptoms, unsteadiness of gait and dysarthia. Disorientation, hallucinations, paranoid ideation, confabulation, impaired self-care, and the commonest neurological features (cerebellar signs, chorea, dystonia, myoclonus, upper motor neuron signs and visual symptoms), develop late in the course of the illness [89]. The duration of disease is longer in vCJD with mean patient survival times of about 14 months [36], compared with about 5 months for classical CJD [21]. Moreover, whereas classical CJD is predominantly a late onset disease with a median age at death of 68 years [21], the median age of onset of vCJD is 26 years [36,89]. The EEG is not helpful in the diagnosis of vCJD, whilst generalised slowing is usually present, the characteristic periodic changes associated with classical CJD are not. The CSF 14-3-3 protein is not helpful, and may often be negative [90]. The most useful non-invasive investigation in advanced cases of vCJD has been MR neuroimaging, particularly the FLAIR sequence [91]. Early case reports noted bilateral increased signal in the posterior thalamus (pulvinar) on T2 weighted images [92]. A retrospective review of MR scans from 36 histologically confirmed cases of vCJD using mainly other forms of human prion disease subjects as controls suggested

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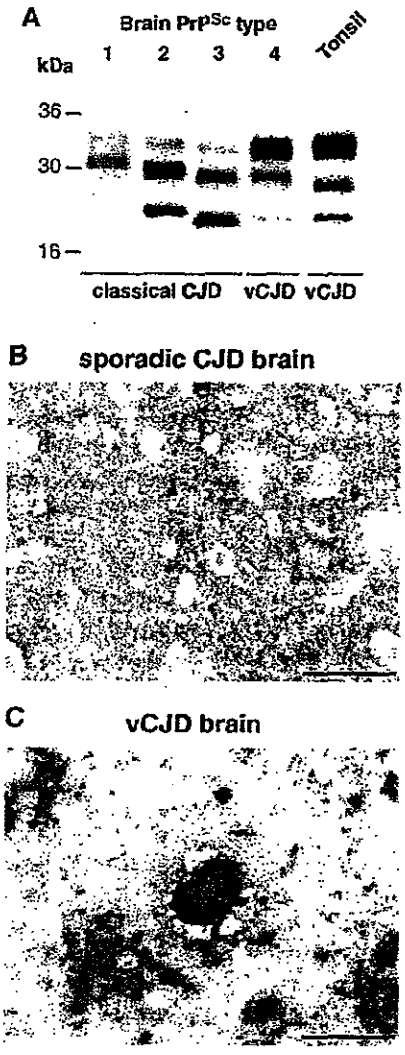

Fig. 1. Characterisation of disease related prion protein in human prion disease. (A) Immunoblots of proteinase K digested tissue homogenate with anti-PrP monoclonal antibody 3F4 showing PrP^{Sc} types 1–4 in human brain and PrP^{Sc} type 4t in vCJD tonsil. Types 1–3 PrP^{Sc} are seen in the brain of classical forms of CJD (either sporadic or iatrogenic CJD), while type 4 PrP^{Sc} and type 4t PrP^{Sc} are uniquely seen in vCJD brain or tonsil, respectively. (B, C) Brain from patients with sporadic CJD or vCJD show abnormal PrP immunoreactivity following immunohistochemistry using anti-PrP monoclonal antibody ICSM35. Abnormal PrP deposition in sporadic CJD brain most commonly presents as diffuse, synaptic staining, whereas vCJD brain is distinguished by the presence of florid PrP plaques consisting of a round amyloid core of PrP surrounded by a ring of spongiform vacuoles. Scale bars B and C, 50 μm.

that the "pulvinar sign" occurred frequently in advanced cases of vCJD [93]. However, histologically confirmed cases of vCJD with minimal or absent pulvinar changes on MR neuroimaging at a mean 10.5 months during an illness of mean 15 months duration were identified in this series. The absence of characteristic MR findings does therefore not exclude a diagnosis of vCJD and more recently figures of 81% sensitivity and 94% specificity have been reported in a series of patients including 27 cases of vCJD diagnosed by tonsil biopsy [94]. As these studies suggest, the pulvinar sign is not specific for vCJD and these MRI appearances are described in sporadic CJD [95], paraneoplastic limbic encephalitis [96] and in a number of rare conditions [97–100]. In contrast, a firm tissue based diagnosis of vCJD can be made during life by tonsil biopsy, with demonstration of a characteristic sub-type of PrP^{Sc} (see below).

6. Molecular basis of phenotypic variability in human prion disease

The marked clinical heterogeneity observed in human prion diseases has yet to be explained. However, it has been clear for many years that distinct isolates, or strains, of prions can be propagated in the same host and these are biologically recognised by distinctive clinical and pathological features [2,101,102]. It is therefore likely that a proportion of clinicopathological heterogeneity seen in sporadic CJD and other human prion diseases relates to the propagation of distinct human prion strains. Within the framework of the protein-only hypothesis of prion propagation, distinct clinical and neuropathological phenotypes are thought to be determined by the propagation of distinct PrP^{Sc} isoforms with divergent physicochemical properties [1,2,9–11,103,104]. Furthermore the propagation of distinct abnormal PrP isoforms may be determined by the host genome [79,105,106].

To date we have identified four major types of human PrP^{Sc} associated with sporadic and acquired human prion diseases that can be differentiated on immunoblots after limited proteinase K digestion of brain homogenates [10,12,15] (Fig. 1). PrP^{Sc} types 1–3 are seen in classical (sporadic or iatrogenic) CJD brain, while type 4 PrP^{Sc} is uniquely seen in vCJD brain [10,12,15]. An earlier classification of PrP^{Sc} types seen in classical CJD described only two banding patterns [11] with PrP^{Sc} types 1 and 2 that we describe corresponding with the type 1 pattern of Gambetti and colleagues, and our type 3 fragment size corresponding to their type 2 pattern [13,107]. While type 4 PrP^{Sc} is readily distinguished from the PrP^{Sc} types seen in classical CJD by a predominance of the di-glycosylated PrP glycoform, type 4 PrP^{Sc} also has a distinct proteolytic fragment size [15] although this is not recognised by the alternative classification which designates type 4 PrP^{Sc} as type 2b [107].

In addition to the identification of distinct human PrP^{Sc} types associated with sporadic and acquired prion disease, molecular strain typing has provided insights into the phenotypic heterogeneity seen in inherited human prion diseases [53,108]. In agreement with existing evidence that human prion strain diversity is generated through variance in PrP^{Sc} conformation and glycosylation, cases of inherited prion disease caused by point mutations have glycoform ratios of PrP^{Sc} fragments distinct from those seen in both classical CJD [108–112] and vCJD [108]. Individuals with the same *PRNP* mutation can also propagate PrP^{Sc} with distinct fragment sizes [108,109,113]. Notably however the detection of PrP^{Sc} in the molecular mass range of ca. 21–30 kDa is by no means a consistent feature. Instead, some cases, in particular those in which amyloid plaques are a prominent feature, show smaller protease resistant fragments of ca. 7–15 kDa [53,108–110,113,114]. The

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