ity of sodium current in both nerve and muscle (*15, 16*). TMO.treatment also causes a reduction of the single-channel conductance of sodium channels of adult nerve (*16, 17*). If the native TTX-resistant (or TMO-treated) sodium channel has a reduced affinity for sodium ions as well as for TTX, then other cations might have greater difficulty entering the channel. Consistent with this view is the observation that TMO-treated single channels are less sensitive to open-channel block by calcium ion (*17*). In fact, TTX-resistant channels are also relatively insensitive to calcium block (*8*). The similarity between TMO-treated and TTX-resistant channels suggests that, in both cases, the altered region for TTX binding is less effective at attracting sodium and calcium ions.

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Human Prion Protein cDNA: Molecular Cloning, Chromosomal Mapping, and Biological Implications

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A human complementary DNA whose protein product is considered to be the major component of scrapie-associated fibrils in Creutzfeldt-Jakob disease, kuru, and Gerstmann-Straussler syndrome has been identified and characterized. The extensive homology of this gene sequence to the hamster PrP 27- to 30-kilodalton prion protein complementary DNA clone, and its existence as a single copy in the human genome, leads to the conclusion that this is the human prion gene. This human prion gene has been mapped to human chromosome 20, negating a direct link between the prion protein and Down's syndrome or the amyloid of Alzheimer's disease.

SCRAPIE IN SHEEP AND GOATS, AND Creutzfeldt-Jakob disease (CJD), kuru, and Gerstmann-Straussler syndrome in humans, have been proposed to represent a group of degenerative encephalopathies caused by a small proteinaceous infectious particle called the prion that is resistant to inactivation by nucleic acid–modifying procedures (*1, 2*). A major protein component of the prion cosediments with hamster scrapie infectivity. This 27- to 30-kilodalton (kD) sialoglycoprotein, designated the prion protein (PrP 27–30), aggregates extracellularly into rodlike structures that resemble amyloid (*2–9*). It has been suggested that this PrP 27–30 component represents an accumulated or altered pathological marker protein that is not an integral part of the infectious agent (*10, 11*). Recently, a PrP 27–30–specific complementary DNA (cDNA) was cloned from scrapie-infected hamster brain (*12*). In addition, a scrapie prion protein–specific messenger RNA (mRNA) was identified in both scrapie-infected and uninfected brain (*13*). To investigate the human counterpart of hamster PrP 27–30 and its possible role in human disease, we isolated homologous cDNA clones, deduced the primary structure of the protein, and mapped the chromosomal location of the gene.

About 100 rat and human clones cross-reacted with two different synthetic oligonucleotide probes (legend to Fig. 1A); if no selection was introduced during cDNA cloning, this represents an mRNA abundance of 0.02% and 0.018% in human retina and rat brain tissues, respectively. Northern blot analysis showed that PrP mRNA is also found in placenta, kidney, vipoma, and neurofibroma. All ten randomly selected positive human clones revealed identical restriction patterns after single and combined digestions with Eco RI, Sac I, and Xba I endonucleases. The three overlapping λ clones with the largest inserts (1.8, 2.4, and 1.6 kb) were subcloned into M13 and the inserts sequenced (Fig. 1).

The cloned and sequenced human PrP 27–30 cDNA contains 2430 nucleotides, including eight poly(A) tail bases (Fig. 2). We translated each human and hamster cDNA in all three possible reading frames and compared all sets of resulting polypeptides. Only one translational reading frame (Fig. 2) of human and hamster cDNA did not contain premature termination and was consistent with the hamster polypeptide sequence. The human PrP cDNA, which has more 5′ sequences than the published hamster sequence, has two methionine codons in the additional 5′ region. We favor the second ATG codon at nucleotide position 84 as the translational start (Fig. 2) because it is

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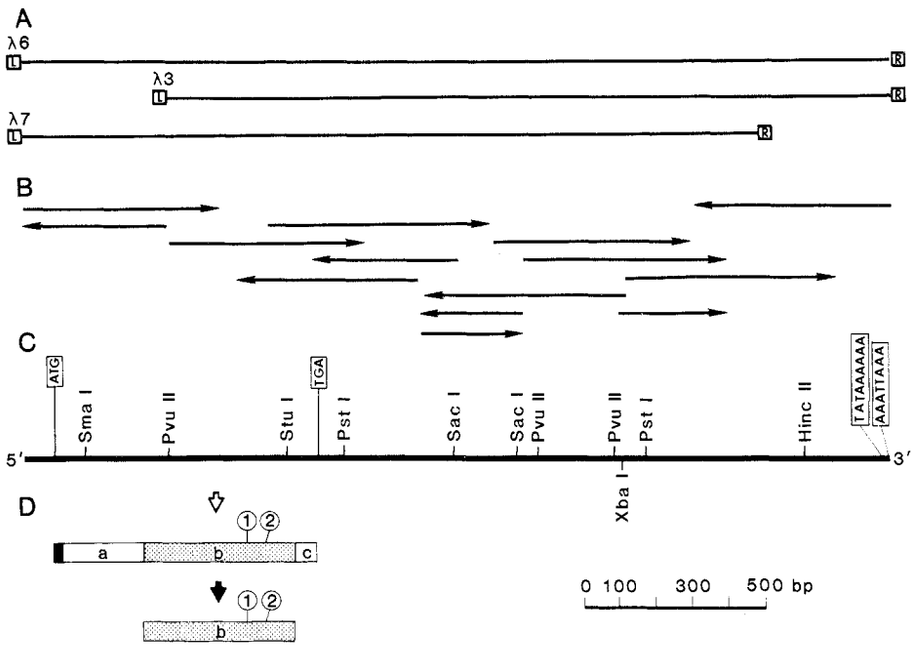

Fig. 1. Human PrP cDNA. (A) Schematic representation of lambda gt10 recombinant clones (lambda 3, 6, 7). L and R represent the left and right arms of bacteriophage lambda, respectively. Two oligonucleotide probes (45 and 23 bases), 5'TGGACTGATGTTGGCCTCTGCAAGAAG-CGGCCAAAGCCTGGAGGG and 5'CTGGGC-AGGGCAGCCCTGGAGGC3', based on the hamster PrP 27–30 cDNA sequence (*12*), were synthesized and radiolabeled by phosphorylating their 5' end with T4 polynucleotide kinase and ^{32}P[ATP]. (B) Nucleotide sequencing strategy. Eco RI–digested endonuclease fragments from lambda clones 3, 6, and 7 were subcloned into bacteriophage M13. The arrows represent the M13 subclones, direction of sequencing, and lengths of sequence data derived by the method of Sanger (*25*) with the use of unique restriction sites for subcloning and a single strand sequencing method (*26*). (C) Restriction map of human PrP 27–30 cDNA. ATG and TGA boxes indicate the translational start and stop codons. Unique common restriction sites on both PrP 27–30 and the M13 polylinker are illustrated. Two potential polyadenylation signals are shown in long boxes at the 3' end. (D) Hypothetical model of human PrP 27–30 formation. A primary translation product was derived (empty arrow) from its corresponding mRNA. The dark region represents the leader signal peptide. The **a** segment is the highly hydrophobic region with sequence repeats of Pro-His-Gly-Gly-Gly-Trp-Gly-Gln. The **b** segment shows potential β conformation and contains two possible glycosylation sites of Asn-Ile-Thr and Asn-Phe-Thr, represented by circles 1 and 2. The **c** segment represents the highly hydrophilic carboxyl terminus. The PrP 27–30 represented by the **b** segment and two carbohydrate side chains are presumed to result from proteinase K digestion at the **a-b** and **b-c** junctions.

```
   1 5'-----CGAGCAGCCAAGGTTCGCCATAATGACTGCTCTCGGTCGTGAGGAGAGGAGAAGCTCGCGGCGCCGCGGCTGCTGG ATG CTG GTT CTC TTT GTG GCC ACA TGG
   1                                                                                      Met Leu Val Leu Phe Val Ala Thr Trp

 111 AGT GAC CTG GGC CTC TGC AAG AAG CGC CCG AAG CCT GGA GGA TGG AAC ACT GGG GGC AGC CGA TAC CCG GGG CAG GGC AGC CCT GGA GGC
  1Ø Ser Asp Leu Gly Leu Cys Lys Lys Arg Pro Lys Pro Gly Gly Trp Asn Thr Gly Gly Ser Arg Tyr Pro Gly Gln Gly Ser Pro Gly Gly

 2Ø1 AAC CGC TAC CCA CCT CAG GGC GGT GGT GGC TGG GGG CAG CCT CAT GGT GGT GGC TGG GGG CAG CCT CAT GGT GGT GGC TGG GGG CAG CCC
  4Ø Asn Arg Tyr Pro Pro Gln Gly Gly Gly Gly Trp Gly Gln Pro His Gly Gly Gly Trp Gly Gln Pro His Gly Gly Gly Trp Gly Gln Pro

 291 CAT GGT GGT GGC TGG GGA CAG CCT CAT GGT GGT GGC TGG GGT CAA GGA GGT GGC ACC CAC AGT CAG TGG AAC AAG CCG AGT AAG CCA AAA
  7Ø His Gly Gly Gly Trp Gly Gln Pro His Gly Gly Gly Trp Gly Gln Gly Gly Gly Thr His Ser Gln Trp Asn Lys Pro Ser Lys Pro Lys

 381 ACC AAC ATG AAG CAC ATG GCT GGT GCA GCA GCT GGG GCA GTG GTG GGG GGC CTT GGC GGC TAC ATG CTG GGA AGT GCC ATG AGC AGG CCC
 1ØØ Thr Asn Met Lys His Met Ala Gly Ala Ala Ala Gly Ala Val Val Gly Gly Leu Gly Gly Tyr Met Leu Gly Ser Ala Met Ser Arg Pro

 471 ATC ATA CAT TTC GGC AGT GAC TAT GAG GAC CGT TAC TAT CGT GAA AAC ATG CAC CGT TAC CCC AAC CAA GTG TAC TAC AGG CCC ATG GAT
 13Ø Ile Ile His Phe Gly Ser Asp Tyr Glu Asp Arg Tyr Tyr Arg Glu Asn Met His Arg Tyr Pro Asn Gln Val Tyr Tyr Arg Pro Met Asp

 561 GAG TAC AGC AAC CAG AAC AAC TTT GTG CAC GAC TGC GTC AAT ATC ACA ATC AAG CAG CAC ACG GTC ACC ACA ACC ACC AAG GGG GAG AAC
 16Ø Glu Tyr Ser Asn Gln Asn Asn Phe Val His Asp Cys Val Asn Ile Thr Ile Lys Gln His Thr Val Thr Thr Thr Thr Lys Gly Glu Asn

 651 TTC ACC GAG ACC GAC GTT AAG ATG ATG GAG CGC GTG GTT GAG CAG ATG TGT ATC ACC CAG TAC GAG AGG GAA TCT CAG GCC TAT TAC CAG
 19Ø Phe Thr Glu Thr Asp Val Lys Met Met Glu Arg Val Val Glu Gln Met Cys Ile Thr Gln Tyr Glu Arg Glu Ser Gln Ala Tyr Tyr Gln

 741 AGA GGA TCG AGC ATG GTC CTC TTC TCC TCT CCA CCT GTG ATC CTC CTG ATC TCT TTC CTC ATC TTC CTG ATA GTG GGA TGA GGA AGG TCT
 22Ø Arg Gly Ser Ser Met Val Leu Phe Ser Ser Pro Pro Val Ile Leu Leu Ile Ser Phe Leu Ile Phe Leu Ile Val Gly

 831 TCCTGTTTTCACCATCTTTCTAATCTTTTTCCAGCTTGAGGGAGGCGGTATCCACCTGCAGCCCTTTTAGTGGTGGTGTCTCACTCTTTCTTCTCTCTTTGTCCCGGATAGGCTAATCAA

 951 TACCCTTGGCACTGATGGGCACTGGAAAACATAGAGTAGACCTGAGATGCTGGTCAAGCCCCCTTTGATTGAGTTCATCATGAGCCGTTGCTAATGCCAGGCCAGTAAAAGTATAACAGC

1Ø71 AAATAACCATTGGTTAATCTGGACTTATTTTTGGACTTAGTGCAACAGGTTGAGGCTAAAACAAATCTCAGAACAGTCTGAAATACCTTTGCCTGGATACCTCTGGCTCCTTCAGCAGCT

1191 AGAGCTCAGTATACTAATGCCCTATCTTAGTAGAGATTTCATAGCTATTTAGAGATATTTTCCATTTTAAGAAAACCCGACAACATTTCTGCCAGGTTTGTTAGGAGGCCACATGATACT

1311 TATTCAAAAAAATCCTAGAGATTCTTAGCTCTTGGGATGCAGGCTCAGCCCGCTGGAGCATGAGCTCTGTGTGTACCGAGAACTGGGGTGATGTTTTACTTTTCACAGTATGGGCTACAC

1431 AGCAGCTGTTCAACAAGAGTAAATATTGTCACAACACTGAACCTCTGGCTAGAGGACATATTCACAGTGAACATAACTGTAACATATATGAAAGGCTTCTGGGACTTGAAATCAAATGTT

1551 TGGGAATGGTGCCCTTGGAGGCAACCTCCCATTTTAGATGTTTAAAGGACCCTATATGTGGCATTCCTTTCTTTAAACTATAGGTAATTAAGGCAGCTGAAAAGTAAATTGCCTTCTAGA

1671 CACTGAAGGCAAATCTCCTTTGTCCATTTACCTGGAAACCAGAATGATTTTGACATACAGGAGAGCTGCAGTTGTGAAAGCACCATCATCATAGAGGATGATGTAATTAAAAAATGGTCA

1791 GTGTGCAAAGAAAAGAACTGCTTGCATTTCTTTATTTCTGTCTCATAATTGTCAAAAACCAGAATTAGGTCAAGTTCATAGTTTCTGTAATTGGCTTTTGAATCAAAGAATAGGGAGACA

1911 ATCTAAAAAATATCTTAGGTTGGAGATGACAGAAATATGATTGATTTGAAGTGGAAAAAGAAATTCTGTTAATGTTAATTAAAGTAAAATTATTCCCTGAATTGTTTGATATTGTCACCT

2Ø31 AGCAGATATGTATTACCTTTCTGCAATGTTATTATTGGCCTTGCACTGTGTAGTATTCTATGTAAAAATATATATGTATATAAAATATATCATTGCATAGGACAGACTTAGGAGTTTTGT

2151 TTACAGCAGTTAACATCTGAAGTGTCTAATGCATTAACTTTTGTAAGGTACTGAATACTTAATATGTGGGAAACCCTTTTGCGTGGTCCTTAGGCTTACAATGTGCACTGAATCGTTTCA

2271 TGTAAGAATCCAAAGTGGACACCATTAACAGGTCTTTGAAATATGCATGTACTTTATATTTTCTATATTTGTAACTTTGCATGTTCTTGTTTTGTTATATAAAAAAATTGTAAATGTTTA

2391 ATATCTGACTGAAATTAAACGAGCCAAGATGAGCACCAAAAAAAAAA-----3'
```

Fig. 2. Nucleotide sequences of the human PrP 27–30 cDNA and the deduced primary protein structure. Nucleotide position numbers in the text correspond to the numbers shown. Seven nucleotides should be subtracted from each position number to correspond to the actual mRNA sequence to take into account the gap in numbering at the 5' end.

followed by hydrophobic amino acids, typical of a leader signal, and because the protein size would be consistent with that of the hamster protein. If the ATG codon further upstream were used as the translational start, an unlikely, highly hydrophilic amino terminal sequence would be transcribed with unusual codons. Our deduced human PrP contains 245 amino acids and has a molecular weight of 26,818 without glycosylation.

After the highly hydrophobic amino terminal sequences, human PrP 27–30 has a polar serine and a highly hydrophilic, negatively charged aspartic acid (position 11). Then an uninterrupted hydrophilic region extends to amino acid position 104 (Figs. 2 and 3). This hydrophilic region contains a striking repeat of short peptide sequences (Table 1) corresponding in both location and sequence to those of hamster PrP 27–30, except for conservative substitutions of glycine (position 49) for threonine and serine (position 90) for asparagine. The first repetitive sequences are Pro-Gly-Gly-Trp-Asn-Thr-Gly-Gly-Ser-Arg-Tyr starting at amino acid position 21, and Pro-Gly-Gln-Gly-Ser-Pro-Gly-Gly-Asn-Arg-Tyr starting at amino acid position 32 (Table 1). The second repeat is represented by a consensus of Pro-His-Gly-Gly-Gly-Trp-Gly-Gln starting at positions 44, 53, 61, 69, 77, and 84 (Table 1). The function of these repeats is unknown, although analogous repeats of Gly-Gly-Gly-X, where X is a hydrophobic amino acid, are found in the amino terminal region of human keratin (*14*) and have been postulated to play a role in β-sheet formation.

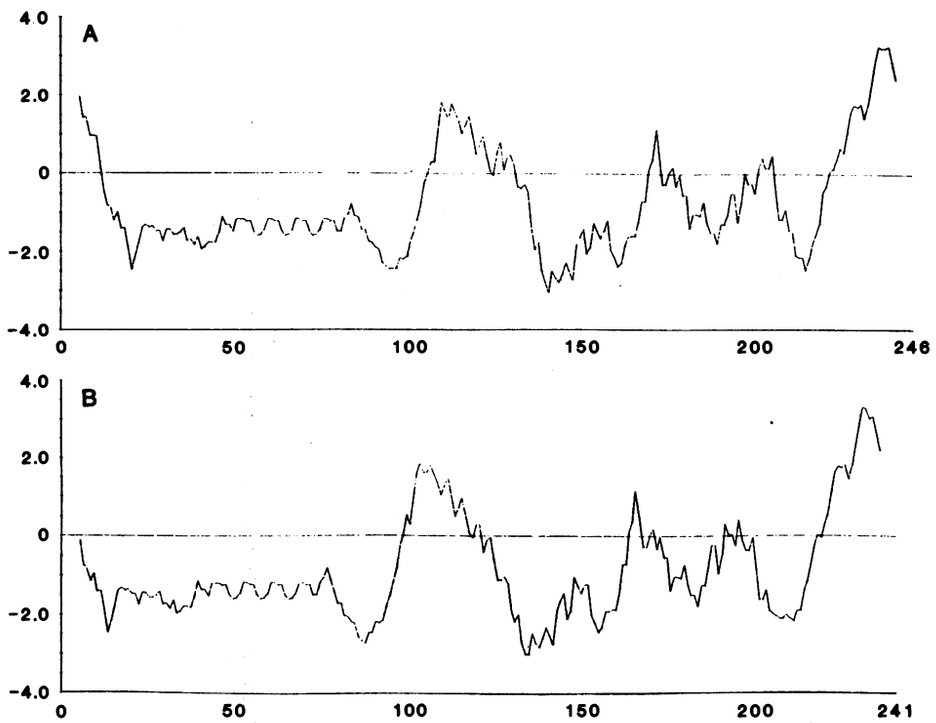

Fig. 3. Hydropathy analysis (*27*) of human (A) and hamster (B) PrP 27–30 protein precursor. The numbers on the *x*-axis indicate the position of amino acid residues. The domains of repeated peptide sequences are located between the leader signal and amino acid 100. These regions are generally hydrophilic and fluctuate in a zigzag fashion.

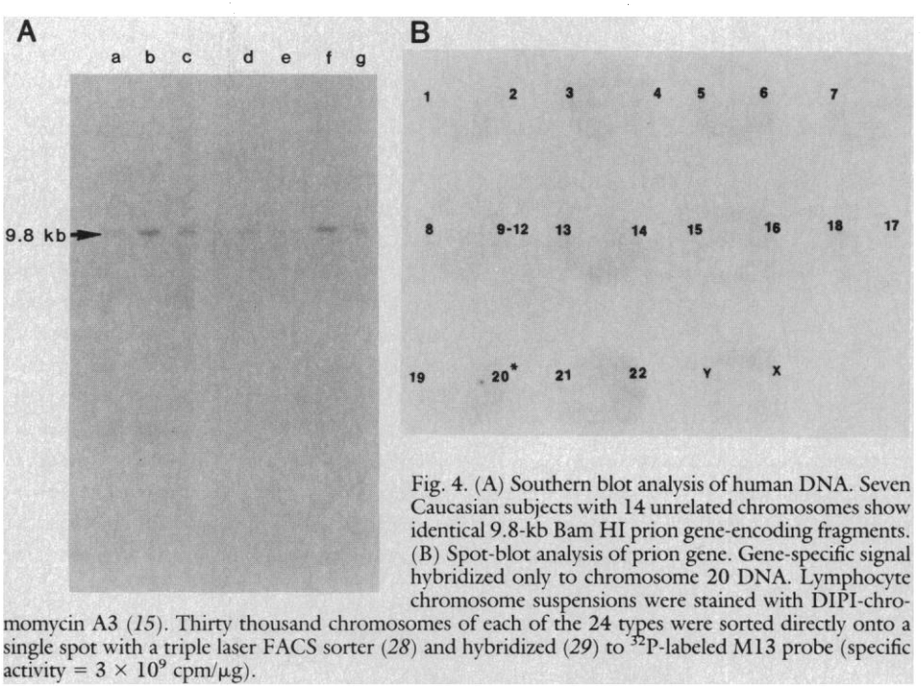

Fig. 4. (A) Southern blot analysis of human DNA. Seven Caucasian subjects with 14 unrelated chromosomes show identical 9.8-kb Bam HI prion gene-encoding fragments. (B) Spot-blot analysis of prion gene. Gene-specific signal hybridized only to chromosome 20 DNA. Lymphocyte chromosome suspensions were stained with DIPI-chromomycin A3 (*15*). Thirty thousand chromosomes of each of the 24 types were sorted directly onto a single spot with a triple laser FACS sorter (*28*) and hybridized (*29*) to ^{32}P-labeled M13 probe (specific activity = 3×10^9 cpm/μg).

The deduced human PrP has two potential N-glycosylation sites of Asn-X-Thr at positions 173 and 189 (Fig. 2). PrP 30–33 has been postulated to be the precursor of PrP 27–30 (*12*). One possible biosynthetic pathway consists of synthesis of the primary translation product of 26,818-dalton cleavage of the signal peptide (Met-Leu-Val-Leu-Phe-Val-Ala-Thr-Trp or longer sequences), and then glycosylation of the protein. It has been suggested that PrP 27–30 is generated when the carboxyl terminal peptide between phenylalanine at position 227 and the end is cleaved by proteinase K during the purification from its precursor (Fig. 1D) (*12*) and has 146 amino acid residues, which is equivalent to the human protein segment of the 144 amino acids from positions 83 to 226. This hypothetical human protein segment with deduced molecular size of 16,422 daltons would contain two carbohydrate side chains of 10,000 to 13,000 daltons if the biosynthetic pathway were correct.

The stop codon TGA is at nucleotide 818. The noncoding region extends to nucleotide 2427, followed by a poly(A) tail. Potential polyadenylation signals of TATAAA and AATTAAA are located at nucleotides 2368 and 2403, respectively. The 3′ noncoding region of human PrP mRNA is about 400 nucleotides longer than the hamster counterpart.

The human PrP coding sequence is contained on a 9.8-kbp Bam HI fragment in all seven individuals investigated (Fig. 4A); single hybridizing fragments are also generated by Sst I and Bgl I. To map the chromosomal location of these fragments, we sorted mitotic chromosome suspensions stained with Hoechst-chromomycin to separate the 24 human chromosome types into 21 fractions (*15*). Filter-bound chromosomal DNA

was denatured and hybridized to our prion gene probe. Gene-specific signals were found only on the spot with chromosome 20 DNA on two complete filter panels (Fig. 4B). These data indicate that a single prion gene per haploid genome is found on human chromosome 20.

Southern blot analyses showed hamster prion cDNA hybridizing to amphibian (frog), invertebrate (insect), and plant (yeast) DNA (*16*). Our data establish that this protein shows 89% sequence homology between the primate (human) and rodent (hamster and mouse) mammalian orders, establishing considerable conservation of this gene over 50 million years of evolution.

Although an 11% difference exists between human and hamster PrP 27–30 amino acid sequences, both retain the β pleated sheet conformation common to amyloids (*17*). This coincidental association of infectivity with the β structure is intriguing. Purified PrP 27–30 is noninfectious (*18*), whereas the aggregated scrapie-associated fibrils are associated with infectivity. Investigators have proposed several hypotheses: (i) that the prion is an infectious agent devoid of nucleic acid, (ii) that the PrP 27–30 protein is a component of the infectious prion, (iii) that the infectious scrapie agent is a typical virus that exists at extremely low titer and is copurified with scrapie-associated fibrils (*19*), or (iv) that the prion is an accumulated or altered pathological protein that can normally reside in, or be derived from, cell membranes (*10*). The 89% homology between rodent and primate prion sequences and the prion mRNA expression we have shown here indicates that the prion gene encodes a protein with an important normal biological function. These results are inconsistent with the first hypothesis and support the fourth hypothesis, but do not address the pathological role of the prion protein in hypotheses (ii) and (iii). Furthermore, the data suggest that the term prion for the infectious entity in related diseases should be considered with care.

The postulated association of Alzheimer's disease and Down's syndrome (*20*) with slow virus infections, such as CJD, kuru, and scrapie (*2*), needs further evaluation. Merz *et al.* (*9*) have shown that, although superficially similar, the amyloid-like structures observed in Alzheimer's disease, CJD, kuru, and scrapie can be distinguished from one another by electron microscopy. The situation is further complicated by the observation that amyloid plaque formation in scrapie is restricted to specific combinations of virus and mouse inbred strains (*21, 22*), whereas the amyloid-like scrapie-associated fibrils are generally found in subacute spongiform virus encephalopathy in the hamster (*8, 9, 23*) and in natural human disease (*9, 23*). Therefore, Braig *et al.* (*21*) have suggested a more general concept of amyloidosis of the central nervous system induced by several different viruses.

The extra human chromosome 21 has been implicated in the increased incidence of Alzheimer's pathology in Down's syndrome, and by further implication to patients with Alzheimer's disease (*20*). Prions comprised of PrP 27–30 kD protein have been suggested to be linked (*2*) to the amyloid of Alzheimer's disease (*24*). A corollary of this reasoning is that prions cause Alzheimer's disease. Our mapping data help to negate this line of reasoning since the PrP gene has been localized to human chromosome 20 and not chromosome 21. Our data do not exclude a more complex interaction between a chromosome 21 gene product and the biosynthesis and degradation of PrP 27–30. The availability of complete PrP cDNA now permits a systematic study of the normal and abnormal biology of this protein.

Table 1. Short peptide sequence repeats in the human prion protein. Numbers show the position in the protein where each sequence starts, numbered from the amino terminus.

21	P	G	G	W	N	T	G	G	S	R	Y
32	P	G	Q	G	S	P	G	G	N	R	Y
44	P	Q	G	G	G	G	W	G	Q		
53	P	H	G	G	G	—	W	G	Q		
61	P	H	G	G	G	—	W	G	Q		
69	P	H	G	G	G	—	W	G	Q		
77	P	H	G	G	G	—	W	G	Q		
84			G	G	G	—	T	H	S	Q	

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