Inherited prion disease with an alanine to valine mutation at codon 117 in the prion protein gene


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Summary

A large English family with autosomal dominant segregation of presenile dementia, ataxia and other neuropsychiatric features is described. Diagnoses of demyelinating disease, Alzheimer’s disease, Creutzfeldt–Jakob disease (CJD) and Gerstmann–Straussler–Scheinker syndrome have been attributed to particular individuals at different times. An Irish family, likely to be part of the same kindred, is also described, in which diagnoses of multiple sclerosis, dementia, corticobasal degeneration and new variant CJD have been considered in affected individuals. Molecular genetic studies have enabled the classification of this disease at the molecular level as one of the group of inherited prion diseases, with the substitution of valine for alanine at codon 117 of the prion protein gene (PRNP). Only three other kindreds have been described world-wide with this mutation and only limited phenotypic information has been reported. Here we describe the phenotypic spectrum of inherited prion disease (PrPA117V). The diversity of phenotypic expression seen in this kindred emphasizes the logic of molecular classification of the inherited prion diseases rather than classification by specific clinicopathological syndrome. Indeed, inherited prion disease should be excluded by PRNP analysis in any individual presenting with atypical presenile dementia or neuropsychiatric features and ataxia, including suspected cases of new variant CJD.

Keywords: inherited prion diseases; prion protein; mutation; molecular genetics

Abbreviations: APOE = apolipoprotein E gene; CJD = Creutzfeldt–Jakob disease; FFI = fatal familial insomnia; GSS = Gerstmann–Straussler–Scheinker syndrome; PRNP = prion protein gene; PrP = prion protein

Introduction

The prion diseases, or transmissible spongiform encephalopathies, are fatal neurodegenerative diseases of humans and animals and include scrapie of sheep and bovine spongiform encephalopathy (BSE) in cattle. They include the clinical syndromes of Creutzfeldt–Jakob disease (CJD), Gerstmann–Straussler–Scheinker syndrome (GSS) and kuru, with the recent addition of fatal familial insomnia (FFI) (for review, see Collinge, 1996). They are characterized pathologically...
by the presence of spongiform change of grey matter, astrocyte proliferation and neuronal cell loss, and in some cases by the presence of amyloid plaques which are immunoreactive with antisera for prion protein (PrP), a host-encoded protein. They can be transmitted experimentally both within and between mammalian species by intracerebral inoculation or sometimes by ingestion of contaminated material. Horizontal transmission routes in humans include iatrogenic inoculation and ritualistic endocannibalism.

The classical clinical presentation of CJD is a rapidly progressive multifocal dementia with myoclonus, proceeding to akinetic mutism and death usually within 6 months. Associated neurological findings include cerebellar ataxia, pyramidal and extra-pyramidal signs and cortical blindness. Behavioural and mood disorders are often present and may precede the dementia. Most cases have a characteristic EEG with periodic sharp-wave complexes. Atypical cases are well recognized. ‘Typical’ GSS has been described clinically as a progressive cerebellar ataxia of earlier onset with the relatively late development of dementia. The clinical course is typically protracted, lasting 5 years on average, but may be much longer. The neuropathological hallmark of GSS is the presence throughout the cerebrum and cerebellum of multicentric amyloid plaques which stain for PrP. Spongiform change may be minimal or absent.

Inherited prion disease—familial CJD, GSS and FFI—accounts for ~15% of human prion diseases and results from autosomal dominant coding mutations in the prion protein gene (PRNP). The study of inherited prion disease has yielded important insights into the molecular mechanisms of these diseases. The first identified pathogenic mutation in the PRNP gene was a 144 bp insertion into the coding sequence in a kindred with familial CJD (Owen et al., 1989, 1996). A second mutation was then described involving a proline→leucine substitution at codon 102 (P102L) in two unrelated families with neuropathologically confirmed GSS, one British and one from the USA. Significant genetic linkage was demonstrated for this mutation, establishing GSS as an autosomal dominant Mendelian disorder (Hsiao et al., 1989). The P102L mutation, absent in the normal population, was rapidly identified in numerous other unrelated GSS kindreds, some individuals presenting in their seventh decade. Incomplete penetrance was reported with the E200K mutation, although recent evidence suggests that penetrance approaches 100% by age 85 years (Meiner et al., 1997).

Most of the inherited prion diseases, including FFI (Brown et al., 1994; Collinge et al., 1995a; Tateishi et al., 1995), have been shown to be transmissible to laboratory animals. These diseases are therefore uniquely both inherited and transmissible. Direct pathogenicity at the molecular level for the P102L mutation has been demonstrated by transgenic mice which over-express a mutant PrP with the analogous mutation to P102L in humans: P101L in mice (Hsiao et al., 1990). Transgenic mice expressing high, but not low, levels of mouse PrP encoding P101L develop spontaneous spongiform degeneration, unlike mice which over-express normal PrP.

A coding mutation for valine rather than alanine at codon 117 (A117V) was first described in a French family with many affected members over several generations. The mutation involves two base changes at codon 117. One of the changes is a non-coding third base polymorphism, A→G, which is present in ~10% of the population. It is easily detected as it destroys a PvuII site in the open reading frame (Wu et al., 1987). The second base change is a coding C→T change, resulting in the substitution of valine for alanine. The mutational event generating the valine-encoding sequence seems to have occurred in a PvuII− allele and thus differs from the normal PvuII+ allele by two bases: GCA→GTG. The same mutation, involving both bases, has since been identified in a US family of German descent (Hsiao et al., 1991) and in an unrelated US family (Mastrianni et al., 1995).

The careful scrutiny of individual cases within these and many other familial CJD or GSS kindreds reveals a broad range of phenotypic presentation extending beyond the classical phenotypes of CJD and GSS. These include atypical dementias, presentations initially more suggestive of other neurodegenerative diseases (Collinge et al., 1992), or with marked neuropsychiatric features (for review, see Mallucci and Collinge, 1997). As specific mutations result in varying clinical pictures that are often far removed from the classical syndromes of CJD and GSS, these conditions may be more logically classified as inherited prion diseases and subclassified by mutation. Indeed, PRNP analysis screening may allow a molecular diagnosis of prion disease to be made, even in cases where the clinical and pathological features would not suggest this (Collinge et al., 1990).

The British–Irish family described here, like the Alsatian A117V family and the English 144 bp insert family, also show a wide range of clinical presentation, varying from Alzheimer-like dementia in middle age to extreme behavioural disturbance and severe cerebellar and extra-pyramidal disorders in individuals in their twenties. Variations in neuropathology are also present. We describe the detailed phenotype of inherited prion disease PrPA117V.

 Patients and methods

Clinical histories

Information on 14 affected family members of the English kindred (family I) and on four affected members of the Irish

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Fig. 1 Family tree of the English pedigree, family I. Closed symbols are affected cases; these include definite cases and cases with fatal neurodegenerative disease who did not come to post-mortem or gene analysis. Open symbols are unaffected cases. Symbols with lines through them represent deceased individuals. Circles represent females and squares represent males; diamond symbols with numbers underneath represent offspring of either sex and their total number. The + symbol marking case II.4 indicates obligate carrier status.

Fig. 2 Family tree of the Irish pedigree, family II. Symbols as for Fig. 1.

Family (family II) has been collected in varying degrees of detail. This ranges from basic information, such as the cause of death stated on death certificates obtained from public records, to detailed clinical, investigative and pathological assessment. Sources include death certificates, hospital records and interviews with relatives. Full neuropathological reports are available on six cases and on histology from a brain biopsy from an additional case. The pedigrees are shown in Figs 1 and 2.

Genealogical investigations
Family lineages were traced back from affected probands. Birth, death and marriage certificates were obtained from the Family Record Centre in London. Where individuals died in hospitals or other institutions the original case notes were used when possible. Other sources of information included interviews with relatives and medical records. The mother of case I.1 in family I (Fig. 1) is known to have been from Ireland, suggesting a link with family II, but no further genealogical data was available on her.

Molecular analysis
DNA was extracted from peripheral blood lymphocytes or brain tissue using standard techniques. DNA was screened for the presence of insertions or deletions in the PrP gene using PCR (polymerase chain reaction) to amplify the entire open reading frame of PRNP avoiding an intron polymorphism as described (Palmer et al., 1996), followed by size-fractionation in agarose gels.

The PCR-amplified PRNP open reading frame was then
Table 1 Clinical features in affected family members

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<th>Case</th>
<th>Sex</th>
<th>Codon 129 genotype (years)</th>
<th>Age at onset (years)</th>
<th>Age at death (years)</th>
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(+ ) = probably present, as in cases where the history is suggestive but features are not documented or where medical notes are unavailable; + = mild; ++ = moderate; +++ = severe; 0 = absent; n/a = not available. *Patient still living; 'M = methionine; V = valine.

sequenced using an ABI 377 automated DNA sequencer to detect known or novel pathogenic mutations and to determine codon 129 genotype (Owen et al., 1990). DNA sequencing to detect several uncommon polymorphisms close to PRNP for haplotype analysis of 700 bp of 5' flanking region and of the entire 3' untranslated region of the gene to the poly(A) tail was performed on DNA amplified using PCR (M. Mahal, A. Dickinson, J. Beck, T. Campbell and J. Collinge, unpublished data).

Apolipoprotein E (APOE) genotype was determined by one-stage PCR followed by CfoI digestion and size-fractionation of products by MetaPhor gel electrophoresis, as described by Wenham and colleagues (Wenham et al., 1991).

Pathological examination
Macroscopic and microscopic examination of post-mortem tissues was performed on individuals III.11, 12, 15 and 16 from family I and on individual iii.6 from family II. Brain biopsy material taken from patient III.20 was examined histologically while the patient was still alive, and again 14 years later when post-mortem results from affected family members became available. Tonsillar biopsy material from patient iii.5 was examined whilst the patient was still alive. Tissue is potentially infectious even after formalin fixation, and it was handled according to established guidelines [Advisory Group on the Management of Patients with Spongiform Encephalopathy Creutzfeldt–Jakob disease (CJD), 1981]. Immunocytochemistry for PrP was performed according to the UK five-centre consensus report (Bell et al., 1997) using antibody 3F4, except for case iii.6, in whom antibody 12F10 (Krasemann et al., 1996) was used.

Results

Clinical findings
The principal clinical features of the illness are summarized in Table 1, and full case reports are provided in Appendix 1.

The central clinical syndrome is of a progressive cortical dementia and varying degrees of cerebellar ataxia. The classic GSS syndrome of progressive cerebellar ataxia with later onset of dementia is observed only in a few cases. Dementia is a dominant, almost exclusive, feature in some patients. Memory loss and cognitive decline was the principal feature in cases II.5, II.6 and II.7, and also in case III.12, who clinically resembled Alzheimer’s disease until the final stages of her illness. In contrast, cerebellar ataxia, dysarthria and incoordination dominates the early clinical picture in cases III.15, III.20, III.22 and III.34, but develops only as a late feature in other individuals. Additional neurological features present in some individuals include a marked extra-pyramidal syndrome giving rise to parkinsonian features relatively early in the clinical course (cases III.15, III.16 and iii.6), and also pyramidal signs, myoclonus, emotional lability and a pseudo-bulbar syndrome.

Relatives had frequently noted the emergence of behavioural and personality disturbance long before the development of neurological symptoms. In some patients mood swings and aggressive and violent behaviour were present for several years before neurological presentation, in sharp distinction to their unaffected siblings. Case III.24 was admitted to a psychiatric unit under section for extreme violent tendencies and paranoia after several years of increasingly aggressive behaviour. Even at this stage, dementia was relatively mild and it was some time before his neurological condition became apparent.
Age at onset of disease and disease duration varies considerably, the youngest case presenting in her twenties and the oldest at 53 years. Individual II.10 died aged 63 years, but no information about his age at onset of disease is available. Most cases presented in their thirties and forties. Individual II.4, a presumed carrier of the mutation, died of unrelated causes aged 50 years; records and interviews reveal him to have been asymptomatic at this age.

Unaffected individuals at the time of writing are symptom-free, and none has been noted to have the similar premorbid personality and behavioural traits displayed by their affected siblings (for details, see Appendix 1). Only one unaffected individual has opted to be screened for the mutation, according to the protocol for presymptomatic testing for Huntington’s disease (Collinge et al., 1991b). Two children of an affected individual declined screening after such counselling.

**Routine investigations**

Biochemical [urea and electrolytes, liver function tests, serum calcium, serum copper, serum ACE (acetylcholine esterase) and serum vitamin B₁₂ and folate levels], haematological [full blood count and ESR (erythrocyte sedimentation rate)], serological (anti-nuclear antibodies, rheumatoid factor, syphilis serology and anti-cardiolipin antibodies) and thyroid function tests were within normal limits. CSF examination, when performed, was normal except for a mildly elevated protein level in case iii.6.

**Electroencephalography**

EEG recordings were either normal or non-specifically abnormal. In no case was the classical pseudoperiodic activity associated with CJD described. Brief summaries of individual findings are given in the appropriate case histories.

**Neuroimaging**

CT scans were performed on eight patients (III.11, III.12, III.15, III.16, III.22, III.24, III.33 and iii.6) and MRI (Fig. 3) on six (patients III.11, III.12, III.22, III.24, III.33 and iii.6). Findings varied from a normal appearance to moderate cerebral atrophy. One case revealed an incidental benign cystic lesion in the right frontal lobe (III.22).

**Genetic analysis**

PRNP analysis was performed on six affected individuals (III.12, III.15, III.22, III.24, III.33 and iii.6) and on one unaffected individual (III.25). All affected patients had the A117V mutation in PRNP on an allele encoding valine at codon 129. Results of genotyping at codon 129 are shown in Table 1, which also shows age at onset and disease duration for all affected cases. The unaffected case was a methionine homozygote at codon 129 and did not have the A117V mutation.

All affected cases from both families were haplotypically identical for several uncommon polymorphisms (S. Mahal, A. Dickinson, J. Beck and J. Collinge, unpublished data) around PRNP, suggesting that the two families were related (data not shown). APOE genotyping gave the following results: five of the six affected cases (III.15, III.22, III.24, III.33 and iii.6) had the ε₃/ε₃ genotype, and one case (III.12) had the ε₂/ε₃ genotype. The unaffected individual had the genotype ε₃/ε₄.

**Pathological findings**

Detailed descriptions of the pathological findings are given for five patients. Macroscopic and microscopic appearances are shown in Figs 4 and 5. Histological features are summarized in Table 2.
Case III.11
The brain weighed 1020 g. There was diffuse cortical atrophy with sulcal widening that was most apparent in frontal and temporal regions. Coronal sections of the hemispheres showed diffuse cortical atrophy, loss of white matter and ventricular dilatation including the third ventricle (Fig. 4). The hippocampi were not conspicuously atrophic. White matter loss was reflected by marked thinning of the corpus callosum and centrum semiovale. The spinal cord, brainstem and cerebellum were macroscopically normal; foliar atrophy was not a feature and the dentate nucleus appeared normal.

Microscopical examination showed widespread degenerative changes. The most conspicuous feature was the deposition of amyloid plaques, particularly in the frontal, insular and temporal cortex and to a lesser degree in the parietal and occipital regions. The plaques showed the predominant involvement of cortical layers 3, 5 and 6, with very few in the outer granular zone. Plaques were very frequent in the hippocampus and subiculum. The plaques were discrete rounded structures comprising an amorphous rim with central stippling. Throughout these regions plaques were not associated with neuritic degeneration and the neuropil adjacent to them was not grossly disrupted. Gliosis was not a feature and focal spongiosis was not a significant component. Many plaques demonstrated simple displacement of neuronal processes around them but were traversed by apparently normal dendrites. In the basal ganglia, however, plaque deposition was associated with neuron loss and gliosis in the caudate, putamen, claustrum and pallidum in decreasing order of severity. In the cerebellum there were small ill-defined plaques and cell loss in the dentate nucleus, and there was widespread demyelination of the cerebellar white matter. In addition, there were infrequent plaques in the superficial molecular layer of the cerebellar cortex which was focally associated with mild spongiosis and gliosis. There was myelin loss from many tracts in the midbrain and brainstem, including the pyramidal pathway at all levels. The substantia nigra showed moderate cell loss with marked incontinence of pigment. Lewy bodies were not a feature. The neuropil showed plaque deposition and focal vacuolation and degeneration of processes. The spinal cord was essentially normal on section.

In silver-stained sections, neurofibrillary tangles, granulovacuolar degeneration and Hirano bodies were not demonstrated. PrP immunohistochemistry performed on sections from the frontal, parietal and occipital neocortex and from the cerebellar vermis and hemispheric cortex showed PrP-immunoreactive structures throughout the grey matter in all these sections, corresponding to the amyloid plaques identified by conventional stains, and the intensity and distribution of these lesions corresponded exactly with those in the sections stained with haematoxylin and eosin.

Case III.12
The brain weighed 1138 g and showed a mild degree of cortical atrophy. The cut surfaces of the cerebral hemispheres showed moderate cortical atrophy with accompanying ventricular dilatation. The cerebellum and brainstem together weighed 178 g, and the cut surfaces showed no evidence of
cerebellar atrophy. The spinal cord was normal both externally and in cross-section.

Sections of the cerebrum and cerebellum showed little evidence of spongiform change. There were numerous plaques within the deep layers of the cerebrum and patchily distributed plaques in the basal ganglia, the thalamus and the molecular layer of the cerebellum, with smaller numbers in the granular layer and cerebellar white matter. Immunocytochemistry for PrP showed strongly positive staining, revealing numerous multicentric plaques with large aggregates of PrP where the plaques appeared to have coalesced to form larger deposits. There was no evidence of an associated neurofibrillary reaction or of perivascular PrP deposition. Plaques were most frequent in the frontal and temporal lobes, the areas of greatest cortical atrophy macroscopically. There was no evidence of coexisting Alzheimer’s disease.

**Case III.15**

Brain weight was not available. External examination showed the brain to be generally small but with no obvious areas of gyral atrophy. The cerebellum and brainstem were also normal on external examination, and the cut surfaces of the cerebrum, cerebellum and brainstem revealed no abnormalities.

Microscopic examination revealed widespread plaque formation with amyloid-like material within the superficial cortical grey matter, particularly in layers 4, 5 and 6, and were most numerous within the frontal and temporal areas. The plaques in these cortical areas appeared to coalesce, forming large masses of amyloid material. Some showed a ‘target’ appearance with a central densely staining core surrounded by a rim of less densely staining material. There was no evidence of spongiform change in the superficial cortex, and astrocytic gliosis and neuronal loss were minimal. There were plaques throughout the deep nuclei, and astrocytic gliosis was particularly marked within the anterior part of the caudate and putamen and within one of the thalamic nuclei. There was no neuronal loss in this region. Myelination throughout the brain was normal. Silver stains revealed no evidence of neurofibrillary tangles and the plaques did not have the morphological features of senile or neuritic plaques. The cerebellum and brainstem appeared relatively spared, with very few plaques. There were, however, small foci of spongiform change within the molecular layer of one cerebellar hemisphere.

**Case III.16**

The brain weighed 1480 g and macroscopic examination was normal. Microscopic examination revealed widespread amyloid plaques within the superficial cortical grey matter, particularly within layers 3, 5 and 6, and most numerous in the frontal and temporal cortical areas. They were also seen within the deep masses of the grey matter and within the molecular layer of the cerebellum. The plaques showed some positive birefringence with polarized light. The plaques in the cortical areas varied in size, some showing a marked ‘target’ appearance of densely staining central core surrounded by less densely staining peripheral rim. Plaque deposition was accompanied by astrocytic gliosis which was minimal within the superficial cortex but particularly pronounced in the anterior part of the head of the caudate nucleus and the putamen. No evidence of neurofibrillary tangle formation or of abnormal neurites within plaques was seen. There was very minimal focal spongiform change within the superficial cortex, and none in the basal ganglia. Examination of the brainstem and spinal cord revealed no abnormality.

**Case III.20**

A brain biopsy performed during the patient’s illness in 1980 was reported to indicate Alzheimer’s disease with numerous senile plaques, but the absence of neurofibrillary tangles. Review of the specimens in 1994 using PrP immunohistochemistry and staining with 3F4 anti-PrP antisera (Kascscack et al., 1987) showed intense staining of the plaques. Immunohistochemistry for βA4 was negative.

**Case iii.6**

The brain weighed 1256 g and had mild generalized atrophy. The neocortex exhibited amyloid plaques, spongiosis and reactive astrocytosis. The plaques were most numerous in the infragranular layers, where they sometimes formed confluent masses. There were fewer plaques in the supragranular layers, where they were unifocal and consisted of a single amyloid granule, a core of amyloid surrounded by smaller granules, or a cluster of amyloid granules alone. The plaques stained positively for PrP using antibody 12F10 (Krassmann et al., 1996) and contained PGM-1-immunoreactive microglial processes and cell bodies, and also APP-immunoreactive distended processes. They were unstained by antibodies to βA4. Ubiquitin staining failed to demonstrate dystrophic neurites associated with plaques, neurofibrillary tangles or neurone processes. The subcortical white matter also contained scattered small plaques. Reactive astrocytosis occurred as a uniform band of cells throughout the molecular layer, and as strongly GFAP (glial fibrillary acid protein)-positive perikarya and processes both around and within amyloid plaques and within the subcortical white matter. Spongiosis occurred focally only in the supragranular cortex to a modest degree.

In the hippocampus the dentate fascia showed scattered plaques in the outer part of the molecular layer. The pyramidal cell layer showed very numerous confluent plaques both in the CA1 zone and the subiculum. Appearances of the parahippocampal gyrus were as for the neocortex. There were scattered PrP plaques and minor spongiosis in the occipital lobe; and in the basal ganglia the caudate, putamen
and globus pallidus all contained numerous PrP plaques and heavy reactive astrocytosis, but no spongiosis.

In the thalamus, the dorsomedial and anterior thalamic nuclei showed numerous PrP plaques but reactive astrocytosis was concentrated in the lateral thalamic nuclei. The internal capsule had foamy macrophages and a large increase in microglia, but myelin staining was within normal limits. The molecular layer of the cerebellum showed rare PrP plaques and no spongiosis, and the folial white matter contained scattered PrP plaques. Purkinje cell and internal granule cell numbers and appearance were normal. These changes were more severe in the cerebellar vermis than in the hemispheres. The dentate nucleus appeared normal and both subfolial and dentate efferent white matter showed very pale staining of myelin. In the pons the corticospinal tract looked pale, but appearances were otherwise normal. The medulla was also normal.

Discussion

This family, in whom dominantly inherited prion disease is shown to be due to a mutation in the prion protein gene PRNP at codon 117, shows wide variation in the clinicopathological features of the disease. Clinical presentation varies markedly between different affected individuals, as does age of onset and disease duration, and there is also variability in neuropathology.

This variability in clinical presentation illustrates the potential for prion disease to masquerade as many other neurodegenerative conditions, particularly within the earlier phases of the illness. Many of the affected individuals in these two families were attributed other diagnoses such as Alzheimer’s disease (case II.12), demyelinating disease (cases II.5, II.9, ii.5 and ii.6), encephalitis lethargica (case I.1), corticobasal degeneration (case iii.6) and cerebrovascular disease (case III.10). Case iii.6 was also, at one stage of her illness, considered to have new variant CJD. Variability of phenotypic expression at the clinical and pathological levels is well established for the inherited prion diseases, and was first described in depth for a family with a 144 bp insertion mutation in PRNP (Collinge et al., 1992) which also showed marked neuroptic features. Many affected individuals described displayed markedly antisocial behaviour, often in the form of violence, hypersexuality or criminality, resulting in their institutionalization, many years before the onset of organic neurological symptoms. In the family with the A117V mutation reported here, case III.20 in particular, and also case III.24, showed similarly extreme behaviour patterns unacceptable socially and even to their own families, long before the development of any recognizable neurological illness. Indeed, neuropsychiatric disturbance such as mood and personality change seems to have been an almost universal occurrence in affected individuals (see cases III.9, III.11, III.12 and III.15) prior to the onset of florid disease.

Age at disease onset (range 26–53 years) and disease duration (range 1–5 years) also vary between individuals. Homozygosity at PRNP codon 129, where methionine or valine can be encoded, increases susceptibility to sporadic (Palmer et al., 1991), iatrogenic (Collinge et al., 1991a) and variant CJD (Collinge et al., 1996); it also reduces age at onset of disease in inherited prion disease with the 144 bp insertion (Poulter et al., 1992) and in inherited prion disease F198S. In inherited prion disease E200K there appears to be no association between age at onset and genotype at PRNP codon 129. Of the six affected individuals in this family whose DNA was analysed (cases III.11, III.15, III.24, III.33 and iii.6), four cases were methionine/valine heterozygotes at codon 129 and two were homozygous for valine. Disease onset for the four heterozygous individuals was in the fifth decade, except for case III.24 who was aged 53 years at onset. The homozygous individuals developed disease at 43 and 26 years respectively. It is of note that the youngest age at onset was in an individual homozygous for valine at codon 129. Data on genotype at codon 129 from other affected individuals with the A117V mutation are needed to establish a relationship between this genotype and age at onset, as seen for some other forms of inherited prion disease.

Genotype at several other loci was also analysed in an attempt to identify any other possible modifying genetic influences on phenotypic expression in this family. APOE genotype analysis was performed due to the known association of earlier disease onset of familial Alzheimer’s disease in individuals with the ε4 allele (Bullido et al., 1998). No association between age at onset and APOE genotype was found in this family. All affected individuals who were analysed were identical for several uncommon polymorphisms at sites in the 5’ flanking region and in the 3’ untranslated region of PRNP, suggesting that these loci do not modify disease expression. However, their identity at these loci is

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**Fig. 5** Sections from the brain of case III.12. (A) Haematoxylin and eosin staining of frontal cortex showing patchy spongiform change and large multicentric plaques appearing as ill-defined eosinophilic structures (centre). (B) Low-power view of the frontal cortex after PrP immunocytochemistry to show multiple plaques throughout the cortex with aggregation at the subpial surface (top). (C) High-power view of the frontal cortex after PrP immunocytochemistry to show multicentric plaques of varying sizes throughout the neuropil, with no particular association with spongiform change. (D) Haematoxylin and eosin staining of the cerebellum shows patchy spongiform change and occasional eosinophilic plaques in the molecular layer (top). (E) PrP staining in the cerebellum shows multiple irregular plaques, some of which form band-like aggregates in the molecular layer. The granular layer is free from plaque formation. (F) High-power view of PrP immunohistochemistry of the cerebellar molecular layer shows multicentric plaques of varying size, some of which form linear aggregates (centre). (G) PrP immunocytochemistry in the basal ganglia shows a composite synaptic and plaque pattern of PrP accumulation with relatively little spongiform change.
strongly suggestive that the English (family I) and the Irish (family II) kindreds are related.

The pathological variation between cases is less marked than the clinical variability, but in one case there was significant cerebral atrophy which was absent in the others. Case iii.6 had florid and often confluent plaque formation, particularly in the infragranular layer of the neocortex, the pyramidal layer of the hippocampus and the basal ganglia. In case III.16 there was marked cerebellar involvement, including white matter degeneration, nuclear atrophy and extensive plaque deposition, whereas in case III.15, whose clinical course was very similar, the cerebellum was very sparsely affected. In none of the cases was there marked spongiosis, and indeed there was minimal or absent spongiform change in four of the five cases examined.

Variability in neuropathology between members of the same family has also been noted in other inherited prion disease families, including the Alsatian family with the A117V mutation, where florid neuritic degeneration and numerous neurofibrillary tangles associated with hyperaggregation of tau protein were noted in one family member only. No such lesions were found in any members of this family.

The pathogenicity of PRNP mutations is inferred from their occurrence only in families with fatal neurodegenerative disease. It is supported by the development of neurological disease and spontaneous neurodegeneration in transgenic mice bearing the P101L mutation (equivalent to the human P102L mutation) (Hsaio et al., 1990). Results from transgenic models of other human PRNP mutations, including the A117V mutation, are awaited.

Transmissibility is a feature of all prion diseases, and transmission of the human prion diseases to laboratory primates (Brown et al., 1994) has been successful for many cases, including the P102L mutation but not for A117V cases. Transmission to wild-type mice has proved difficult to show for many human prion isolates (Tateishi et al., 1980, 1981), but the development of transgenic mice expressing human PrP, but not mouse PrP, which lack a species barrier to human prions and are highly susceptible to CJD (Collinge et al., 1995b; Telling et al., 1995), has provided a mouse model for transmission studies. Using these mice, the transmission of many isolates of the human prion diseases, including many of the inherited forms, has been achieved (Collinge et al., 1995a, 1996; Hill et al., 1997).

The traditional clinicopathological classification of the prion diseases into GSS, CJD and FFI has clear limitations. We have suggested that the inherited prion diseases should be classified according to mutation alone without specific syndromic definitions (Collinge et al., 1990, 1992). An alternative subclassification was proposed by Hsaio on reporting the second family to be described with the A117V mutation (Hsaio et al., 1989). Affected individuals both in this family and in the first A117V mutation family reported (Doh-ura et al., 1989) had phenotypic features diverging from classical GSS, including pseudobulbar and extra-pyramidal syndromes, the A117V mutation giving rise to ‘ataxic GSS’ and the P102L mutation giving rise to ‘atypical GSS’ with cerebellar pathology.

However, in the third family to be reported with the same mutation (Mastrianni et al., 1995) many affected members had marked early cerebellar symptoms and frank cerebellar pathology at post-mortem. As we have shown for the fourth reported family with the A117V mutation, marked variability at both the clinical and the neuropathological level is characteristic of inherited prion disease, and indeed is observed in some families with the P102L mutation, including the original Austrian family described by Gerstmann (Doh-ura et al., 1989; Brown et al., 1991; Speer et al., 1991; Kretzschmar et al., 1992).

Thus, attributing clinical syndromes even to different PRNP alleles may result in ‘atypical’ cases being missed. The family reported by Hsaio had originally been thought to be a familial Alzheimer’s kindred (Heston et al., 1966) prior to the identification firstly of PrP staining in amyloid plaques in post-mortem specimens (Nochlin et al., 1989) and then of the A117V mutation on PRNP analysis (Hsaio et al., 1989). Similarly, screening for PRNP mutations in families with ataxia and dementia where prion disease was not suspected revealed the presence of pathological PRNP mutations in two cases (Collinge et al., 1989b).

The identification of a PRNP mutation in an individual

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age at death (years)</th>
<th>Brain weight (g)</th>
<th>Atrophy loss</th>
<th>Spongiosis</th>
<th>Neuronal plaques</th>
<th>Astrocytosis plaques</th>
<th>Amyloid</th>
<th>PrP</th>
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<tr>
<td>III.11</td>
<td>F</td>
<td>44</td>
<td>1020</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
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<td>+++</td>
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<tr>
<td>III.13</td>
<td>F</td>
<td>46</td>
<td>1138</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
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<td>28</td>
<td>n/a</td>
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<td>–</td>
<td>+</td>
<td>+</td>
<td>+ +</td>
<td>n/a</td>
</tr>
<tr>
<td>III.15</td>
<td>M</td>
<td>34</td>
<td>1480</td>
<td>–</td>
<td>( )</td>
<td>–</td>
<td>+</td>
<td>+++</td>
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<tr>
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<td>F</td>
<td>39</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
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(Brain biopsy)

1980
1994

iii.6 F 45 1256 + + – + ++ + + + + + ++

Table 2 Histological features of affected cases
with a neurodegenerative disease is easily performed on a blood sample (with informed consent), and obviates the need for invasive diagnostic procedures such as brain biopsy, tonsil biopsy for variant CJD or for post-mortem neuropathological diagnosis. Finding such a mutation has profound implications for individuals and their families. Presymptomatic testing or antenatal screening can be undertaken after counselling according to guidelines established for Huntington’s disease (Collinge et al., 1991b).

The genetic analysis of inherited prion disease gives rise to new concepts in the diagnosis and classification of neurodegenerative disease. The variability in phenotypic expression of the A117V mutation described here, and of other PRNP mutations previously reported, emphasizes the fact that single genetic mutations can have protein manifestations. These are often similar to those of other genetic, but also of some sporadic, neurodegenerative disorders. Inherited prion disease needs to be considered in the differential diagnosis of any atypical presenile dementia or ataxic illness in a young person, particularly if seen in association with neuropsychiatric features: it is one of the important differential diagnoses of new variant CJD (Will et al., 1996). The identification of PRNP mutations as the cause of neurological disease and the continued exploration of the prion diseases at the molecular level may elucidate some of the mechanisms involved in infectivity, strain variability and neurodegeneration in these diseases, and across the spectrum of neurodegeneration.

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References


Appendix 1
Clinical description of affected family members

Family I
I.1. Male born 1888. Died aged 50 years of postencephalitic paralysis according to death certificate.
I.2. Female. Died aged 75 years of ‘old age’. She was otherwise well.
I.3. Female. Died of bone cancer, aged 46 years. She was otherwise well.
I.4. Male, born 1915. Died at the age of 50 years of carbon monoxide poisoning. This occurred at a convalescent home where he was recovering from duodenal ulcer surgery. A gas flue had broken in the bathroom. The coroner’s report recorded death by misadventure. He had been a boilermaker’s mate, had married in 1937 and had eight children. There is no record of neurological disturbance or of any other symptoms.
I.5. Female, born 1925, died in 1953 aged 28 years, having been diagnosed as having multiple sclerosis.
I.6. Female; died in her forties of dementia.
I.7. Female, born 1918. She had been admitted to the local asylum at the age of 40 years with a 4-year history of progressive personality change and general intellectual deterioration. On examination she had been found to have severely impaired recent and remote memory, to be emotionally labile, and had also increased muscle tone, exaggerated tendon reflexes and severe dysarthria and ataxia. An EEG had shown slowing in the left occipital region, and an air encephalogram had shown dilatation of both ventricles, the left more than the right. She had died a few months later. Recorded cause of death was myocardial failure due to aortic incompetence, with chronic purulent bronchitis and mental deficiency as contributing factors.
I.10. Male, born 1929. Died aged 63 years. Cause of death documented on death certificate was given as cerebrovascular accident with dementia as a contributing factor. Age of onset of disease and disease duration are unknown.
I.12. Female born 1939. She married in 1963 aged 24 years and had a son. She developed severe mood swings and bouts of aggression and was thought to be of a ‘nervous disposition’. She is recalled as having thrown her baby son down some steps in fury when not allowed to join her parents and two youngest siblings on a holiday. She was aged 26 years at the time. Outbursts of violence were fairly frequent, but she recovered quickly and was oblivious to their effects on people. From the age of 28 years, 5 years before her death, she became increasingly unsteady and fell frequently. She was thought by local people to be drinking heavily. In the last 2 years she developed a severe dementia and profound limb ataxia. She became immobile and severely wasted. She was diagnosed as having multiple sclerosis prior to her death aged 33 years.
I.14. Female, born 1945. Died aged 44 years. In the years prior to presentation she had become moody and aggressive. She presented with the relatively rapid development over 1 year of a progressive cerebral degeneration with unsteadiness on her feet, memory problems, changes in her speech and feelings of dizziness when walking. A CT head scan had shown diffuse cerebral atrophy only and an EEG had been felt to be within normal limits. Other investigations had been unhelpful. She deteriorated steadily and, in contrast to her affected siblings, had become obese prior to her death, gaining around 4 stones in her final months. She died of pyelonephritis in hospital. Post-mortem findings are described above.

III.10. Female, born 1950. She had died aged 45 years. She had presented at the age of 43 years with dementia. She had become increasingly moody and aggressive in the years prior to presenting, and had become involved in physical fights with one of her daughters. Clinically, she had a global dementia, confirmed by psychometric testing. Indeed, her presentation was felt to be consistent with early-onset Alzheimer’s disease. Within a few months, however, subtle cerebellar signs had begun to emerge, with impairment of heel–toe gait on examination; she also exhibited the occasional startled response. PRNP gene analysis revealed the codon 117 alanine→valine mutation. Her ataxia deteriorated significantly over the ensuing months and she became dysarthric. She developed myoclonus and a degree of fidgetiness bordering on chorea. Her cognitive function and immobility deteriorated inexcusably. She died 4 years after the onset of the illness.
III.11. Female, born 1958. She has been well until the last 3 months, during which she has complained of non-specific symptoms. Neurological examination was normal.
III.12. Female, born 1962. She presented, aged 27 years, with a 6-month history of speech and walking difficulties. She had had many falls and was injuring herself frequently; she was unable to walk unaided at presentation. In the months leading up to presentation it was noted that she was increasingly unable to cope with writing letters and with fairly minor tasks, despite having had a secretarial post for a year before the birth of her first child. She had also experienced bouts of aggression and had sought help for her violent impulses towards her child. Her family described her behaviour as increasingly aggressive for several years prior to presentation. On examination, she had dysarthria, mask-like facial expression, ataxic gait and signs of mild pyramidal weakness in the left leg. Dementia was marked. Within weeks of her initial presentation she was admitted for the first of a series of respite admissions. Her condition continued to progress inexorably, with immobility, marked extra-pyramidal signs, extreme emotional lability and dysphagia. She was admitted to hospital for long-term care and died 6 months later aged 28 years.
III.13. Male, born 1955. He had presented at the age of 33 years with a 1-month history of slurring of speech and difficulty in walking. Initial examination revealed generalized myoclonus, and widespread cerebellar deficits and corticospinal signs. Dementia was mild at this stage. He also had mask-like facies and showed perseverating movements of his legs. He was admitted for long-term care within 2 months of his initial presentation in view of his increasing disability. His ataxia became so severe that poor trunk control limited his ability to mobilize and even to sit at all. He developed profound impairment of swallowing and died of bronchopneumonia 15 months after admission, aged 34 years.
III.14–19. Two females and one male. It has not been possible to interview these individuals but they are thought to be well by their relatives.
III.14. Male, born 1940. She had excelled at dancing as a girl and young woman and had won many shields and medals. She had left the family and her village at the age of 15 years to live with an older man in a nearby town. This man had fairly recently arrived in Britain from an ethnic background very different from hers and her family disowned her as a result of the relationship. She had an illegitimate son by him, but the relationship had ended soon after

Inherited prion disease A117V
the birth. She gave up her son to his father, who returned to his own country with him. She had later married a local man, and had a daughter in 1969. She had then divorced and remarried within a few years. She continued to have very little contact with her own family. Social services had been involved with her daughter from the age of 8 years. In 1978, she was pregnant with her third child and had applied for her 9-year-old daughter to be taken into care before the new baby was expected. Soon after the birth, now aged 38 years, she had developed dysarthria, and then ataxia with marked difficulties in walking. Over the next 6 months she was admitted to hospital suffering from memory problems and numerous falls. She was found to have cerebellar signs, emotional lability, increased tendon reflexes and bilateral extensor plantar responses. A diagnosis of multiple sclerosis was considered. Both children were taken into care. Her condition worsened over the next year and she developed severe dementia. She needed full-time nursing care until her death, in hospital, aged 40 years. She had been diagnosed as having Alzheimer's disease, on the basis of a brain biopsy which showed numerous senile plaques but 'the absence of neurofibrillary tangles'. Review of the slides and staining with PrP antisera 14 years later revealed the correct diagnosis of prion disease.


III.22. Female, born 1943. She presented at the age of 52 years to an ENT surgeon with a 1-year history of increasingly poor balance with repeated falls following an ear infection. The first symptom that she complained of had been inability to get out of a car unaided when attending the funeral of her brother (case III.24, below). Marked gait ataxia was noted on examination at this stage. Neurological referral some weeks later revealed her to have impairment of memory and other higher mental functions, emotional lability and the presence of primitive reflexes. She had marked gait apraxia and gait ataxia. There was minimal limb ataxia and intention tremor. Pyramidal signs were absent. Within 3 months she had developed tingling in her calves and was unable to walk and Unable to stand unaided. She had developed generalized myoclonus and pyramidal signs with mild rigidity, hyper-reflexia and extensor plantar responses. She also had marked cerebellar incoordination, profound trunk and gait ataxia. Neuropsychometric testing showed marked language impairment, memory impairment for verbal and non-verbal material, frontal lobe and visual–perceptual impairment, finger agnosia and impaired body orientation restricted to extra-personal space errors. An EEG showed marked regular and irregular slow activity, particularly in the left frontotemporal regions. An MRI scan of her brain showed marked global atrophy well in excess of normal for her age and a cystic lesion of undetermined significance in the right frontal lobe. Screening of peripheral blood for PRNP mutations revealed the codon 117 alanine–valine substitution. The patient is currently akinetic and mute in a nursing home.


III.24. Male, born 1946. He died, aged 48 years, in 1994. He had left school at 16 years and had various jobs, his last being as a manual labourer. He had last worked 3 years before his death when he was sacked from a job on a major building scheme. He had married at the age of 22 years and had three children. His personality had changed in the years before presentation, as he became increasingly moody and 'inappropriate and insensitive'. His medical records at the local hospital reveal several presentations from the age of 18 years, but particularly in his thirties, when he presented with fractured ribs and a broken nose (on two occasions) sustained in fights, and at other times with a head injury and a hand laceration. His married life had become difficult after about 10 or 15 years; he displayed increasingly aggressive and argumentative behaviour towards his wife. His memory was felt by those close to him to have been subtly impaired for many years, but in the months before he presented he had been found wandering at night (by day he would have forgotten why he had left the house) and he repeated himself unnecessarily during conversation. All aspects of his behaviour and memory loss had become increasingly marked in the 9 months prior to his admission under section 2 of the Mental Health Act (1983), aged 46 years, to the psychiatric wing of his local hospital. He had been threatening the lives of his family. Examination at this time had shown him unwilling to admit anything was ‘wrong’ with him, and he had no insight that his behaviour was irrational or abnormal in any way. He was prone to outbursts of anger and irritability during questioning, but otherwise the admitting psychiatrist had been struck by his 'apathetic demeanour and vacant stare'. He had a Mini-Mental score of 27/30, positive primitive reflexes, but no other localizing signs. An EEG was normal but a CT brain scan showed early atrophic changes, confirmed on MRI. PRNP gene analysis confirmed the pathological codon 117 alanine–valine mutation. He became increasingly demented, ataxic and immobile over the following 2 years. He developed severe dysphagia and pseudobulbar palsy, and urinary incontinence. He became mute 6 months before he died, at home, needing constant nursing care.

III.25. Female, born 1947. She developed severe heart failure in her late forties and the family noticed a deterioration in her memory. PRNP gene analysis, both by ASOH and by automated sequencing, revealed no mutation in the PRNP gene, and a post-mortem confirmed death to have resulted from congestive cardiac failure due to cardiomyopathy. There were no neuropathological findings.


III.27–32. Four females, two males born in the 1960s. All are believed to be well.

III.33. Female, born 1954. She presented at the age of 40 years with a 6-month history of progressive unsteadiness of gait, slurred speech and mild deterioration in her memory. On examination, mentation was slow but her answers to questions were sensible. There were no involuntary movements; she had positive primitive reflexes; her eye movements and speech showed cerebellar deficits. She also had an ataxic gait and demonstrated diminished coordination and dysdiadochokinesis in all limbs. She had pyramidal signs in her legs, with increased tone and extensor plantar reflexes. All routine investigations were normal or negative, other than a CT brain scan which showed cerebral atrophy excessive for her age. An EEG was of low voltage but otherwise normal. PRNP gene analysis demonstrated the presence of the codon 117 alanine–valine mutation. Her disease progressed over the following 2 years with increasing immobility and dysphagia, although she retained a degree of insight into her condition and remained relatively orientated. She was admitted for long-term care 6 months prior to her death in February 1998.

iii.34–38. Three males, two females. Well.

Family II

i.1. Male, died in his fifties; cause of death unknown. Very few details are available and he is poorly remembered by surviving relatives.

i.2. Female, died aged 72 years of ‘old age’.

ii.1. Male, died of cancer aged 74 years.

ii.2. Male, died of chronic bronchitis in his late fifties.
iii.3. Female, thought to have died after an epileptic fit in her thirties. She is survived by three children, one of whom has epilepsy.

ii.5. Male, died in his late forties. He had emigrated as a young man, and was believed to have died of multiple sclerosis in his adopted country.

ii.6. Female, died in her forties, having been diagnosed as having multiple sclerosis.

ii.9. Female, aged 60 years. Well.

iii.1–4. Two males and two females. All aged between 40 and 50 years. All are well other than the presence of epilepsy in case iii.1.

iii.6. The patient presented at the age of 43 years with weakness of the left arm and a limp in her left leg. Over the ensuing months she experienced general cognitive decline especially affecting short-term memory. Examination 1 year after onset showed impairment of short-term memory, distractability, flat affect, dysarthria, dystonic posturing of the left arm and dystonic movements of the left leg, and myoclonic jerking of the left limbs. She had bilateral blepharoclonus and a supranuclear up-gaze palsy. There was increased tone in the limbs, and a predominantly pyramidal distribution of weakness in all limbs, more marked on the left. Tendon reflexes were brisk and the left plantar reflex was extensor. There were left-sided cerebellar signs in the limbs, dysarthric speech and also apraxia of the left hand. Primitive reflexes were elicited. An MRI scan showed mild, generalized cortical atrophy. CSF examination was normal other than a mildly raised protein level. Diagnoses of corticobasal degeneration and either variant or inherited CJD were considered. Tonsillar biopsy was performed. PRNP gene analysis revealed the presence of the A117V mutation. Over the following months she developed a left-sided ptosis and increasing spasticity and weakness of the limbs; generalized myoclonic jerking was present at rest which was very stimulus-sensitive. She suffered a progressive decline in her condition and died at the age of 45 years.

iii.8, iii.10, iii.12. Three males; all well.

iii.13. Female, died of cancer aged 18 years.

Generation iv: Four males and four females, aged between 18 and 30 years. All are well.