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Familial Alzheimer's disease

A pedigree with a mis-sense mutation in the amyloid precursor protein gene (amyloid precursor protein 717 valine → glycine)

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SUMMARY

Ten affected individuals are described from a kindred with autosomal dominant familial Alzheimer's disease in which a mutation in the amyloid precursor protein gene results in a valine to glycine substitution at amyloid precursor protein 717 which co-segregates with the disease. The mean age at onset of symptoms was 52 years with a range from 40 years to 67 years. The median duration of the disease was 11 years, with a range of 7–16 years. All individuals fulfilled the National Institute for Neurological and Communicative Disorders and Stroke criteria for probable Alzheimer's disease. A homogeneous clinical and neuropsychological pattern was evident within the family. Myoclonic jerks, seizures, depression and a lack of insight were common features. Positron emission tomography demonstrated biparietal bitemporal hypometabolism in the one affected individual who was studied. The diagnosis was confirmed histopathologically in one individual.

INTRODUCTION

Alzheimer's disease may be familial in as many as 10–45% of cases (Fitch *et al.*, 1988; Farrer *et al.*, 1989). Since the first descriptions of familial Alzheimer's disease (Schottky, 1932; Lowenberg and Waggoner, 1934) a number of large pedigrees have been described in which there is an autosomal dominant pattern of inheritance (McMenemey *et al.*, 1939; Feldman *et al.*, 1963; Heston *et al.*, 1966; Cook *et al.*, 1979; Goudsmit *et al.*, 1981; Nee *et al.*, 1983; Bird *et al.*, 1988; Frommelt *et al.*, 1991; Martin *et al.*, 1991). More recently, genetic linkage with chromosome 21 has been demonstrated (St George-Hyslop *et al.*, 1987; Goate *et al.*, 1989) and subsequently three distinct point mutations in the amyloid precursor protein gene at codon 717 were shown to co-segregate with the affected individuals in chromosome 21 linked families. A mutation resulting in a valine to isoleucine substitution was first shown in one British and one American kindred (Goate *et al.*, 1991) and later amyloid precursor protein 717 phenylalanine (Murrell *et al.*, 1991) and amyloid precursor protein 717 glycine substitutions (Chartier-Harlin *et al.*, 1991) were reported. The presence of three different mutations at codon 717

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suggests that these are indeed pathogenic and provides evidence for allelic heterogeneity at this site. However, not all families show linkage to chromosome 21, indicating additional genetic heterogeneity in this condition (Schellenberg *et al.*, 1988; St George-Hyslop *et al.*, 1990).

The many detailed clinical descriptions of familial Alzheimer's disease pedigrees have highlighted a variety of features including myoclonus (Lowenberg and Waggoner, 1934; Feldman *et al.*, 1963; Cook *et al.*, 1979; Fukutani *et al.*, 1989; Patel, 1989; Frommelt *et al.*, 1991), seizures (Lowenberg and Waggoner, 1934; McMenemy *et al.*, 1939; Feldman *et al.*, 1963; Cook *et al.*, 1979; Fukutani *et al.*, 1989; Frommelt *et al.*, 1991), extrapyramidal signs (Feldman *et al.*, 1963; Goudsmit *et al.*, 1981) and prominent aphasia and apraxia (Breitner *et al.*, 1984). Some reports give insufficient clinical details and only a small number of cases have been examined prospectively. These two factors make analysis of the clinical features of familial Alzheimer's disease difficult. It is not clear which, if any, are specific to familial Alzheimer's disease and indeed how they relate to the more common sporadic form of the disease. In addition, phenotypic heterogeneity has been observed in some families and was thought to reflect presumed genetic or allelic heterogeneity (Bird *et al.*, 1989), although until recently the underlying genetic defects had not been identified. We therefore present the clinical, neuropsychological and neuroimaging features of the three living affected subjects and the available clinical information on the seven deceased individuals in the British kindred with the amyloid precursor protein codon 717 valine to glycine substitution. These features are compared with the published familial Alzheimer's disease kindreds.

METHODS AND PATIENTS

Family overview

The family tree is shown in Fig. 1. Information is available for 10 affected individuals (seven males and three females) spanning three generations. The pattern of inheritance is autosomal dominant. Cases I.1

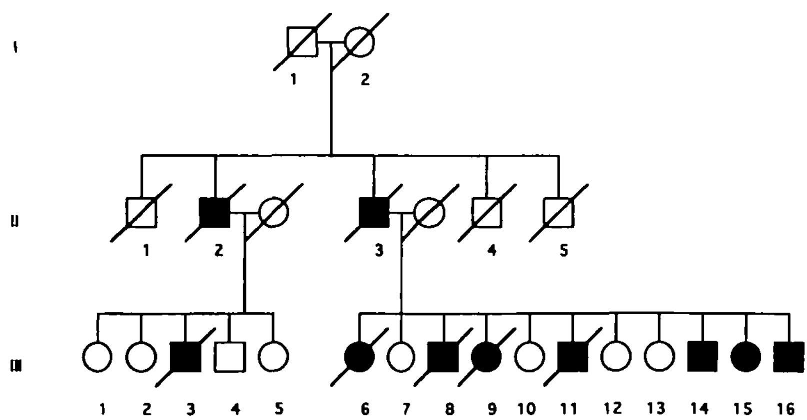

FIG. 1. The family tree showing that the pedigree spans three generations and affects a total of 10 individuals. Post-mortem confirmation of Alzheimer's disease has been provided in II.9.

and I.2 died at the age of 80 years and 55 years, respectively. Both were not known to be affected and according to medical records died of ischaemic heart disease and cancer of the liver, respectively. There was no history of cognitive impairment or neurological illness in either case. Three individuals are still living and were available for further study. Direct sequencing of exon 17 of the amyloid precursor protein gene revealed a T−G transversion at base pair 2150 changing valine to glycine at position 717 of the amyloid precursor protein transcript (Chartier-Harlin *et al.*, 1991). This mutation co-segregates with affected individuals in the family and was not found in 24 other pedigrees sequenced. The median age at onset is 52 years with a range from 40 years to 67 years (mean = 52 ± 7.8 years SD). The duration of the disease from onset to death varied from 7 years to 16 years.

Methods

Details concerning deceased individuals were obtained from case records and where possible the unaffected siblings of an affected family member were interviewed. The age at onset, duration and age of death were determined. Age at onset was defined as the age at which family members considered an individual to be first definitely affected by the disease. Neuropathological confirmation of Alzheimer's disease was made in patient III.9 who underwent post-mortem examination, details of which have been published elsewhere (Mann *et al.*, 1992).

All living affected individuals underwent neurological assessment including the Mini Mental State examination (Folstein *et al.*, 1975), Blessed Dementia Rating (Blessed *et al.*, 1968) and Clinical Dementia Rating (Hughes *et al.*, 1982) in addition to detailed neuropsychological assessment. The National Institute for Neurological and Communicative Disorders and Stroke criteria for Alzheimer's disease were applied (McKhann *et al.*, 1984; Tierney *et al.*, 1988). Details of the neuropsychological tests are given in Appendix 1. One individual underwent positron emission tomography (PET) using $[^{18}F]$fluorodeoxyglucose in order to calculate regional cerebral glucose metabolism.

Ethical approval for this study was obtained from the local ethics committee at all coordinating hospitals. Signed consent for all investigations and procedures was obtained from the general practitioner, next of kin and carer of each patient.

RESULTS

The age at onset and clinical features are summarized in Table 1 and Fig. 2. Detailed case reports for all individuals are given in Appendix 2.

Case III.16 had the earliest age at onset of 40 years whereas Case II.2 is recorded as having an age at onset of 67 years. The median is 51 years. Case III.11 had an episode of depression at the age of 40 years, before developing cognitive impairment at the age of 45 years. All cases demonstrated prominent memory impairment initially and the disease had a progressive but indolent course. However, Case III.14 appeared to show fluctuations. Visuospatial impairment was the second most prominent symptom

TABLE 1. AGE AT ONSET/CLINICAL FEATURES OF PEDIGREE

Subject (No.)	*Age at onset (years)*	*Age at death (years)*	*Age examined (years)*	*Duration of disease (years)*	*First symptoms*	*Second symptoms*	*Other symptoms*	*Depression*	*Seizures*	*Myoclonus*
II.2	67	73	–	7	Repeating self	Recognition	Visuo-spatial	0	0	–
II.3	49	61	–	12	Memory	Visuo-spatial	Personality	0	+	–
III.3	59	74	–	15	Memory	–	–	0	+	–
III.6	55	61	–	–	Memory	–	–	+	0	–
III.8	Not known	62	–	–	Not known	–	–	–	–	–
III.9	53	61	–	8	Memory	Visuo-spatial	–	+	0	–
III.11	45	61	–	16	Depression	Memory	Visuo-spatial	+	+	+
III.14	50	–	61	10+	Memory	Visuo-spatial	Personality change	+	+	+
III.15	51	–	58	8+	Word finding	–	–	0	+	+
III.16	40	–	55	15+	Memory	Visuo-spatial	Personality change	+	?	+

This table summarizes the clinical features for each individual in pedigree.

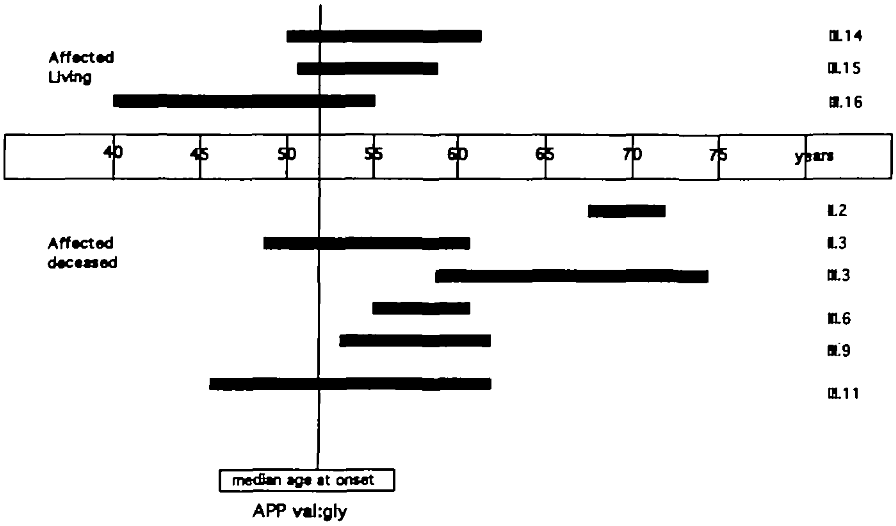

FIG. 2. The age at onset and duration of illness for each living and deceased affected individual is indicated as a solid horizontal bar. The median age at onset is 52 years.

in six out of the 10 individuals. Three individuals had documented hypertension (III.6, III.9, III.11) and two had severe ischaemic heart disease (III.9, III.11). Five of the individuals had seizures and two had attacks of disequilibrium of undetermined origin. All living affected patients had myoclonic jerks, and myoclonus had been reported in one other individual.

DISCUSSION

The early age at onset, myoclonic jerks, seizures and depression which are salient features of this family have been observed frequently in familial Alzheimer's disease. Lowenberg and Waggoner in 1934 described five individuals from a family who had the clinical and pathological features of Alzheimer's disease. Their index case, a 32-year-old printer, was described as 'peculiar and unbalanced mentally' and subsequently developed memory problems and childish behaviour. He had a number of documented seizures and was noted to have myoclonus. Two of his sisters similarly had seizures and 'muscular twitchings of the myoclonic type'. Early speech and gait disturbance was observed in this kindred. Subsequent studies have described large pedigrees in which myoclonus, seizures and extrapyramidal features are frequent but not invariable findings. Indeed some reports have documented features that would put the diagnosis of Alzheimer's disease in doubt by National Institute for Neurological and Communicative Disorders criteria (Heston *et al.*, 1966).

Table 2 summarizes the clinical features of familial Alzheimer's disease pedigrees which have been published in detail previously. The ages at onset for these families range from 33 years to 68 years, the median being 46 years (mean = 45, SD ± 10.1 years). The mean duration within families varied from 3 years to 15 years with a median

TABLE 2. SUMMARY OF PUBLISHED FAMILIAL ALZHEIMER'S DISEASE PEDIGREES

References	*Family code or country*	*Mean age at onset (years)*	*Range of age at onset (years)*	*Mean duration (years)*	*Range of duration (years)*	*Total cases (no.)*	*Detailed cases (no.)*	*Pyramidal signs (no.)*	*Extrapyramidal signs (no.)*	*Myoclonus (no.)*	*Seizures (no.)*	*Apraxia (no.)*	*Depression (no.)*	*Histology (no.)*
Lowenberg and Waggoner (1934)	USA	34	32–36	4	2–6	5	5	0	0	3	4	0	1	2
McMenemey *et al.* (1939)	UK	56	50–63	4	–	3	1	1	0	1	0	0	0	1
Feldman *et al.* (1962)	USA	38	35–47	3	1–5	13	10	0	4	4	4	2	2	4
Heston *et al.* (1966)[a]	NY	36	22–53	3	1–7	17	4	3	2	1	0	0	0	4
Landry *et al.* (1970)	Australia	41.5	40–43	3	–	3	1	1	0	0	0	1	0	2
Cook *et al.* (1979)	R	49	40–68	12	6–23	14	7	0	1	4	2	2	0	4
Cook *et al.* (1979)	K	46.5	44–48	8	4–13	4	0	0	–	–	–	–	–	1
Goudsmit *et al.* (1981)[b]	SW	48	42–54	–	6–18	21	10	1	0	0	0	0	0	10
Goudsmit *et al.* (1981)	MP	46	42–48	–	2–10	14	8	0	4	0	0	0	0	0
Nee *et al.* (1983)[c]	Canadian	46	40–50	8	–	51	3	0	0	0	0	0	0	4
Bird *et al.* (1988)[d]	KS	67	62–76	9	5–17	9	4	1	0	0	0	1	0	1
Bird *et al.* (1988)[e]	H	60	58–61	15	9–22	8	2	1	1	0	0	0	0	1
Bird *et al.* (1988)	W	52	48–58	11	6–19	4	1	0	1	0	0	0	0	1
Bird *et al.* (1989)	MG, BB, CEW, L, V	42	30–51	8.8	1–23	42	0	–	33%	13%	13%	–	–	49
Bird *et al.* (1989)	P, HLP, WLA, CSF, MI, JR, BH, T	68	59–78	8.5	–	34	0	–	21%	6%	3%	–	–	–
Bird *et al.* (1989)[f]	CDH	60	50–63	–	–	1	1	–	1	0	1	–	–	–
Bird *et al.* (1989)[g]	CSF	62	58–66	–	–	–	–	–	–	–	–	–	–	–
Bird *et al.* (1989)[h]	BK	50	35–65	11	–	–	0	–	Tremor	–	–	–	–	–
Sadovnick *et al.* (1988)[i]	Scottish	38	36–40	6	4–5	12	1	0	0	1	0	–	2	4
Patel *et al.* (1989)	UK	58	53–62	9	7–14	3	3	0	1	1	0	2	0	0
Fukutani *et al.* (1989)[j]	Japan	33	33–36	9	4–12	1	1	0	1	1	1	0	0	1
Martin *et al.* (1991)[k]	Belgian A	35	26–45	6.4	3–12	40	0	0	Common	Common	Common	0	0	11
Martin *et al.* (1991)	Belgian B	34	30–39	6.8	3–13	24	0	Common	0	Common	Common	0	0	6
Karlinsky *et al.* (1991)	Canadian	47	43–54	10	6–16	13	5	0	0	0	1	0	0	2
Frommelt *et al.* (1991)[l]	German	47	39–55	7	7–12	21	12	0	7	5	6	0	0	3

A total of 25 pedigrees published in the English literature are listed chronologically with the relevant family code name when indicated. The number of cases within each family for which detailed neurological features are available are indicated and the number of cases with individual features recorded. [a] Two cases had positive VDRL; [b] one case had ALS, one had Down's syndrome and one had Parkinson's disease; [c] one case possible non-penetrance; [d] one had Parkinson's disease but normal cognition; [e] non-penetrance in one case and CVA in another; [f] *état-criblé* in one case; [g] anterior horn cell pathology; [h] schizophrenia symptoms early, one had Downs syndrome; [i] one autopsy case had PET scan; [j] gait ataxia noted; [k] cerebellar ataxia; [l] linkage to C21 and three had PET scans.

of 7.5 years. Extensive clinical details have been given for some pedigrees (Lowenberg and Waggoner, 1934; Feldman *et al.*, 1963; Cook *et al.*, 1979; Goudsmit *et al.*, 1981; Sadovnick *et al.*, 1988; Bird *et al.*, 1989; Frommelt *et al.*, 1991) and with the single exception of the family described by Feldman *et al.* (1963), myoclonus and seizures are prominent in all. Depression has been documented in only four pedigrees (Lowenberg and Waggoner, 1934; Feldman *et al.*, 1963; Heston *et al.*, 1966; Sadovnick *et al.*, 1988). Extrapyramidal features occur in some pedigrees but are less frequent than seizures and myoclonus (Feldman *et al.*, 1963; Bird *et al.*, 1989). A case of amyotrophic lateral sclerosis and Parkinson's disease is noted in the absence of cognitive impairment in two families (Goudsmit *et al.*, 1981; Bird *et al.*, 1988) and one family had schizophrenic symptomatology in addition (Bird *et al.*, 1989). Stroke was only observed in one individual despite the presumably high incidence of amyloid angiopathy in these patients (Bird *et al.*, 1988). A variety of atypical findings have been recorded. Heston *et al.* (1966) found pyramidal signs in their family and others have documented ataxia (Fukutani *et al.*, 1989; Martin *et al.*, 1991). Possible non-penetrance has been recorded only twice (Nee *et al.*, 1983; Bird *et al.*, 1988).

The amyloid precursor protein 717 valine to glycine family presents a number of clinical features that are similar to Lowenberg's original cases, including myoclonus and seizures. Nearly all patients have an insidious impairment of recent memory with prominent visuospatial symptoms occurring early in the disease. Personality change often follows this and aggressive outbursts are noted subsequently. Unlike Lowenberg and Waggoner's cases, language is affected relatively late in the course of the illness.

Myoclonus was a prominent clinical finding in all three living individuals that were examined and is a feature of other families that we have studied. Frommelt *et al.* (1991) found myoclonus within 3 years of onset and indeed they report this in six out of 13 cases they reviewed. A number of authors have suggested that the presence of myoclonus may reveal a subtype of Alzheimer's patients (Feldman *et al.*, 1963; Chang Chui *et al.*, 1985; Mayeux *et al.*, 1985). Mayeux *et al.* (1985) noted that patients with myoclonus were younger at onset, but no reference is made to the presence of a family history in these cases. Recently, myoclonus, seizures and extrapyramidal features have been assessed by cumulative risk analysis during the progression of sporadic Alzheimer's disease (Chen *et al.*, 1991). Psychosis and extrapyramidal features were found to be more common early in the disease but myoclonus was found to have an equal prevalence in the later course of the disease. This does not support the earlier hypothesis that myoclonus characterizes a subtype of sporadic Alzheimer's disease, but a number of studies suggest that the situation is different in familial Alzheimer's disease where myoclonus can be a prominent and early sign (Frommelt *et al.*, 1991; Martin *et al.*, 1991).

Similarly Frommelt *et al.* (1991) found an increased prevalence of seizures in their families, particularly in those patients with myoclonic jerks, whereas Romanelli *et al.* (1990) found seizures appeared late in sporadic Alzheimer's disease occurring in 16% of his cohort. All of these patients had generalized tonic clonic seizures and there was no association with myoclonus. Five of our cases had episodes of disturbed consciousness which were thought to be epileptic and the least affected case (III.16) had a number of episodes of disturbed consciousness compatible with complex partial seizures but without electroencephalogram (EEG) confirmation. Two patients reported an olfactory aura suggestive of temporal lobe phenomena, although there is no available EEG confirmation of a temporal lobe focus in either of these cases. The published literature suggests that seizures may occur early in familial Alzheimer's disease—indeed in one of Lowenberg and Waggoner's cases a single seizure preceded the cognitive impairment. Two of our patients had a history suggesting epilepsy on presentation and two patients had attacks that were thought to be anxiety attacks which were prominent early manifestations of the disease.

Case III.15 had lifelong, non-progressive left-sided neurological deficit which was observed and described as 'a congenital hemiparesis' when assessed by her local neurologist in 1985. Although focal motor deficits have been reported in familial Alzheimer's disease, the focal signs in this case are not felt to be due to the Alzheimer's disease since they predate the cognitive impairment by several decades.

By contrast, depression has been documented relatively infrequently in familial Alzheimer's disease (Bird *et al.*, 1989), although psychiatric phenomena occur frequently in sporadic Alzheimer's disease. Indeed Burns *et al.* (1990) noted that depression occurred in 43% of their cohort and was associated with milder cognitive impairment. An episode of depression predated the illness in Case III.14 and a total of four of our patients had depressive symptoms. The relationship of these features to the early stages of the disease is important as one might suppose that the presence of insight may predispose to depression. However, all individuals demonstrated little in the way of insight even early in the disease.

The two individuals that we were able to study in detail were both moderately affected. Despite this they both had a long history of gradual cognitive decline. They presented with memory difficulty and had marked visuospatial problems early in the course of the disease. Their speech was relatively preserved and they could both give an account of themselves. The neuropsychological profiles of the two individuals were similar. Language skills (Oldfield, Vocabulary subtest of the WAIS-R, and reading) are relatively spared in the light of poor spelling skills. Both showed dyscalculia and poor memory.

All previous studies of affected family members within familial Alzheimer's disease pedigrees have reported deterioration of both 'recent' and 'remote' memory as the major neuropsychological feature (Sadovnick *et al.*, 1988; Karlinsky *et al.*, 1991; Nee *et al.*, 1983). Our investigations and collected case reports would support this broad notion but are limited with regard to further specification due to the severity of the disease in the living affected subjects. Dyscalculia has previously been reported as a feature of familial Alzheimer's disease and our findings provide further evidence for this (Nee *et al.*, 1983; Karlinsky *et al.*, 1991).

Sadovnick *et al.* (1988) and Karlinsky *et al.* (1991) showed impairment in confrontation picture naming in affected individuals from similar pedigrees. The relatively intact performance of III.14 and III.16 on the Oldfield Picture Naming test (Oldfield and Wingfield, 1965) directly contrasts with these observations. This may be due in part to the more sensitive testing that we administered. Direct comparison of other findings with those documented in the literature are impossible because of the disease duration and test administration differences. However, the most fruitful way to compare the features of different families is likely to be by examination of the earliest presenting features.

Earlier work has suggested that the age of disease onset is tightly grouped within familial Alzheimer's disease (van Duijn *et al.*, 1991). Our pedigree shows some variability in age at onset ranging from 40 years to 67 years (SD = 7.8 years; variance = 68). The relevance of the variation in age at onset from one family to another needs to be treated cautiously. Estimates of age at onset are, however, difficult and progressive decline may have been present for many years before medical help was sought, as in Case II.2, although the relatives report the age at onset as 67 years. Anticipation is likely to occur in subsequent generations due to increased awareness of family members and the opportunity for detailed documentation. If the amyloid precursor protein mutations determine age at onset then epigenetic factors will be important in determining the variation in age at onset within a given family. Thus the observation that age at onset may be more variable in some pedigrees provides an opportunity to determine important environmental factors that may be contributory. Despite the observed variation, no obvious factor stands out in this family.

Positron emission tomography has been shown to demonstrate a biparietal and bitemporal pattern of hypometabolism in Alzheimer's disease (Frackowiak *et al*, 1981; Friedland *et al.*, 1983). The typical PET findings described in our case would support the notion that this pattern has some specificity for Alzheimer's disease. A number of authors have described PET findings in individual case reports of patients with familial Alzheimer's disease (Cutler *et al.*, 1985; Polinsky *et al.*, 1987; Sadovnick *et al.*, 1988; Adams *et al.*, 1989; Bird *et al.*, 1989) but there is no large series of autosomal dominant familial cases reported. The patient reported here was severely affected and a symmetrical scan and frontal involvement would be in keeping with the severity of the dementia in this patient (Frackowiak *et al.*, 1981). No asymmetry was observed despite the hemispheric differences inferred from the neuropsychological data.

Three mutations at the amyloid precursor protein 717 locus have now been identified (Chartier-Harlin *et al.*, 1991; Goate *et al.*, 1991; Murrell *et al.*, 1991), although it is not clear whether differing amino acid substitutions lead to different clinical features. The reported clinical features of amyloid precursor protein 717 valine to isoleucine and valine to phenylalanine mutations are broadly similar with an age at onset in the early fifties and mid-fifties, respectively (Hardy *et al.*, 1991; Farlow *et al.*, 1992). Myoclonus has been observed in both mutations. One autopsied case with amyloid precursor protein 717 valine to isoleucine mutation had cortical Lewy bodies but this is not a consistent feature (Lantos *et al.*, 1992). A mis-sense mutation at amyloid precursor protein 693 resulting in a glutamate to glutamine substitution is associated with Hereditary Cerebral Haemorrhage with Amyloidosis—Dutch Type (Levy *et al.*, 1990). This results in a very different clinical phenotype in that there is a severe amyloid angiopathy leading to recurrent cerebral haemorrhage and diffuse parenchymal deposits of β A_4 amyloid protein but none of the cytoskeletal pathology of neuritic plaques or neurofibrillary tangles seen in Alzheimer's disease. Recently, a mutation at amyloid precursor protein 692 resulting in an alanine to glycine substitution has been reported in a Dutch family (Hendricks *et al.*, 1992). Some family members suffered cerebral haemorrhages, whereas others developed a progressive dementia. A cerebral biopsy in one case with haemorrhage revealed amyloid angiopathy, sparse neuritic plaques and no neurofibrillary tangles.

In addition to the observed allelic heterogeneity at the amyloid precursor protein locus there is evidence of genetic heterogeneity with chromosome 21 linked and non-linked families (Schellenberg *et al.*, 1988; St George-Hyslop, 1990). A number of features suggest that there may be a characteristic phenotype in our pedigree and seizures, myoclonus and the lack of insight have consistently been observed. However, other features, particularly the age at onset, appear more variable. More detailed comparison of the features at presentation and subsequent course of the differing amyloid precursor protein mutations will establish whether such heterogeneity is associated with specific clinical phenotypes.

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(See overleaf for Appendices)

APPENDIX 1

Descriptions of the tests administered

WAIS-R (Weschler Adult Intelligence Scale, revised edition) (Weschler, 1981). A shortened version was administered. A verbal and performance IQ was prorated from scores on the Digit Span, Vocabulary, Arithmetic and Similarities subtests and performance IQ was prorated from scores on the Picture completion. Picture arrangement and Block Design subtests.

NART (National Adult Reading Test) (Nelson, 1991). This reading test, consisting of 50 irregular words was administered to provide an estimate of premorbid intelligence and their combined scores were transformed into full-scale IQ equivalents.

Recognition Memory Test (Warrington, 1984). The verbal version of this test consists of 50 stimulus words. Recognition memory was tested by presenting each of the words paired with a distractor, the subject being required to make a forced choice between them. The visual version of this test consists of 50 black-and-white photographs of unfamiliar male faces. The subject was asked to recognize them when each was paired with a distractor photograph drawn from a similar pool. The raw scores for both versions were converted into age-corrected percentile scores.

Graded naming test (McKenna *et al.*, 1983). This object-naming test of graded difficulty consists of 30 black-and-white line-drawings. The number of objects correctly named was converted into an equivalent vocabulary percentile score.

Oldfield Picture Naming (Oldfield and Wingfield, 1965). This object naming test consists of 30 line-drawings of objects, including six very common names.

British Picture Vocabulary Scale (Dunn *et al.*, 1992). This single word auditory comprehension test consists of 150 words. Subjects have to match the spoken word to one of four pictures. Raw scores were converted into percentile scores.

Arithmetic test (Jackson and Warrington, 1986). This graded difficulty test of oral arithmetic consists of 12 graded difficulty additions and 12 graded difficulty subtractions. A 10 s time limit is imposed for each sum, after which the answer is incorrect. The raw score was converted into a percentile score.

Spelling test (Baxter *et al.*, 1987). This oral spelling test consists of 30 irregularly spelt words, graded in difficulty. The raw scores covert into percentile scores.

Visual Object and Space Perception Battery (Warrington and James, 1991). Silhouettes subtest consists of 15 animal and 15 object stimuli. This graded difficulty test is comprised of black silhouettes of each item rotated through varying degrees from the lateral axis. Cube Analysis subtest: this graded difficulty test of visuospatial skills consists of 12 black outline representations of a three-dimensional arrangement of square bricks. Subjects have to count the number of cubes in the structures according to standard administration. Both these subtests' raw scores were converted to percentile scores.

Speed tests: Cancelling A's and Battery B (Willison *et al.*, 1980). The first test consists of rows of different letters randomized and containing A's on an A4 sheet. The task is to put a line through every A on the page as quickly as possible. Digit copying (Battery B): this consists of rows of randomly assorted single digits, which the subject has to copy in his or her own handwriting. The responses to these two tests are timed and the results converted into percentile scores.

Weigl Colour-form sorting task (Weigl *et al.*, 1941): An abstract sorting task consisting of 12 shapes; three circles, three triangles, three squares, each shape is represented in one of four colours. The subject has to sort the items twice: once according to shape and once according to colour. Standard instructions were given.

APPENDIX 2

Detailed Case Reports

Affected (deceased)

II.2. (Age at onset 67 years and age at death 73 years.) This right-handed miner spent the last year or more of his life in a psychiatric hospital. No clear diagnosis was ever established. His daughter recalled that at the age of 67 years her father failed to recognize her and this was taken by the family to be the age at onset. It is possible that his wife had remarked on her husband's poor memory and his tendency to repeat himself some 2 years earlier. He had not worked in the mine since the age of 45 years owing to pulmonary tuberculosis; otherwise his past medical history had been unremarkable.

His speech was preserved until the time of his death, although he would not strike up conversation spontaneously. For a long time he had been unable to find his way about the house and his wife had to direct him to the lavatory. He was described as being 'moody' and often rather obstinate, but at no time was he aggressive. There is no record of seizures or myoclonic jerks. He was, according to his daughter, more mildly affected than his brother II.3. No clinical records survive.

III.3. (Age at onset 59 years and age at death 74 years.) This right-handed miner presented with a 4-year history of increasing forgetfulness at the age of 63 years. He was noted to be unable to recall information only minutes after being told items of importance. Although always described as 'forgetful', this problem had undoubtedly worsened over the preceding 3 years. He retired aged 62 years on account of his difficulties, but remained independent at home by himself, although he had problems with everyday activities. For instance, the electricity meter was often found full of coins as he would forget that he had fed the meter only hours earlier. He had visuospatial difficulties and was unable to locate items of furniture in the house by himself.

He was described as being shy, often anxious and at times depressed, subsequently becoming uncharacteristically aggressive. He demonstrated little insight into the extent of his predicament and he frequently apologized for having a 'bad memory'. He thought his problem resulted from an incident when he was hit on the head by a rifle during the war. In recent times a loss of consciousness was noted but no further details were provided as to whether this was a seizure. He complained of continuous frontal headache, which he described as a cold around the head. He was admitted to an old people's home for the last 6 years of his life.

Examination of the cranial nerves was normal and no primitive reflexes were elicited. Wasting of the limbs was noted, but the rest of the examination was unremarkable apart from withdrawal on eliciting the plantar responses and a positive Romberg's sign. There is no record of myoclonic jerks. He was disorientated and had difficulties with arithmetic.

An isotope brain scan suggested an avascular blush but a subsequent computerized tomograph (CT) was normal apart from mild cerebral atrophy. Haematological and biochemical parameters were normal including negative treponemal serology. The serum vitamin B_{12} was below normal and he was started on regular replacement therapy. The chest X-ray showed signs of old tuberculosis. No post-mortem examination was performed.

III.6. (Age at onset 55 years and age at death 61 years.) At the age of 58 years, this left-handed shopkeeper was admitted to hospital for neurological assessment following a 3-year history of insidious cognitive decline. There was no relevant past medical history. She was unaware of the purpose of the admission, although she volunteered that she had a mild memory problem. Her son recalls her persistently asking the price of items in the shop and repeating the same questions. She had been intermittently depressed, but there had been no change of personality or any additional neurological symptoms. There was no history of loss of consciousness or seizures.

Neurological examination revealed that she was disorientated in time, but not place and was unable to name the prime minister or remember three objects after 3 min. The hospital records suggest 'some evidence of constructional apraxia but no dressing apraxia'. The speech was said to be normal at this time. Investigations were normal including vitamin B_{12}, folate, thyroid function tests, CSF examination and treponemal serology. An EEG showed a poorly sustained alpha rhythm and air encephalography showed cerebral atrophy.

Neuropsychological assessment revealed a verbal IQ of 74 and a performance IQ of 59. She found it difficult to understand what was required of her and her vocabulary was recorded as being significantly better than her digit span, comprehension or similarities.

Her speech had deteriorated in the last 2 years of the illness and she became incontinent of urine. At the age of 61 years she was admitted to a local hospital. At this time she was noted to have difficulty finding her way about. She made no conversation but continued to recognize her family. She was described as being 'twitchy', but there is no specific record as to the presence of myoclonic jerks. The death certificate states that she died at the age of 61 years from an 'arterial cerebral haemorrhage'. No post-mortem was performed and no other details are available.

III.8. [Age at onset (not known) and age at death 62 years.] Little is known about this member of the family who emigrated to Australia. He returned to the United Kingdom for a family wedding and was noted to be forgetful. During this visit he became lost when he went to the shops to purchase some cigarettes. He was unable to find his way home and was returned hours later by the police. He died at the age of 62 years in Australia.

III.9. (Age at onset 53 years and age at death 61 years.) This right-handed factory supervisor was made redundant at the age of 53 years after failing to cope with the introduction of a new work practice. Her past medical history was unremarkable but she was reported to be intermittently depressed, and she had often used minor tranquillizers such as diazepam.

It was clear that for some time her husband covered up for her memory difficulties and her son recalls her losing her way home from the hairdresser at the age of 53 years. She also experienced what were thought to be anxiety attacks. During one of these, she sat down because she felt dizzy and described a 'sensation in her solar plexus'. There was no history of associated loss of consciousness or convulsions.

At the age of 57 years her husband was unexpectedly admitted to hospital, and she was sent to stay with her son because of her inability to cope by herself. She was more severely affected than the family had imagined. She was unable to find the lavatory and was found in the bath trying to dry herself whilst the bath was still full of water. When given some talcum powder she threw it over the floor and had no comprehension of its purpose. At this time when she met an acquaintance in the street she would stand speechless and repeat the last words spoken to her. By the following year she was mute. She experienced a number of falls resulting from 'bad' coordination and she suffered a fractured nose and elbow as a result. Her daughter-in-law describes a probable startle reponse but there was no documentation of myoclonus.

Post-mortem examination was performed and the typical features of Alzheimer's disease were found as previously reported (Mann *et al.*, 1992). The brain weighed 1230 g and showed diffuse deposits of β A_4 protein throughout the cortex. Neuritic plaques and tangles were common in all cortical regions including hippocampus and amygdala. No other inclusion bodies were seen, but severe congophilic angiopathy was noted.

III.11. (Age at onset 45 years and age at death 61 years.) This right-handed miner presented at the age of 40 years with a sudden episode of depression, which resolved spontaneously after 6 months. At this time he described suicidal ideation and felt that he was at risk of putting his head in the gas oven. He had a morbid fear of being admitted to the local psychiatric hospital where his father had died of dementia. His past medical history was unremarkable apart from two myocardial infarctions.

Five years later at the age of 45 years, he developed memory problems. He had difficulties about the house such as forgetting the names of objects, an inability to recall what seeds he had planted in his garden and difficulty locating the light switches. People at work would make fun of him and he was put on light duties having lost himself on a number of occasions at the coal face. The discharge summary states that he had major seizures and also at times would suddenly appear vacant. These episodes were preceded by what he described as the 'death smell', although there was no history of associated stereotyped movements or *déjà vu*. His personality changed and he became aggressive and jealous; frequently accusing his wife of infidelity. He would have considerable difficulty sitting down and would walk around the chair before trying to sit. He was unable to use a tape measure or cutlery. At the age of 56 years he was assessed neurologically and a CT brain scan showed cerebral atrophy. Vitamin B_{12}, thyroid function and treponemal serology were all normal or negative. An EEG demonstrated a lack of alpha rhythm.

Three years prior to his death he was admitted for long-term psychiatric care. At this stage he was incontinent of urine and faeces and had to be fed. He was mute for the last 2 years of his life and preterminally had difficulty in swallowing. He was noted to be hypertensive with an average blood pressure of 160/110. His wife describes spontaneous and startle induced jerkings consistent with myoclonus.

The death certificate states that he died of left ventricular failure. No post-mortem examination was performed.

Affected (living)

III.14. (Age at onset 50 years.) This 61-year-old left-handed steel worker had a 10-year history of cognitive disturbance which was first recognized when he started arriving at work for the wrong shift. He was made redundant and despite losing his job continued to attend for work. He was unable to handle his financial affairs and would discard a £10 note as being worthless. The condition slowly worsened. His wife reported some day-to-day fluctuations with a more accelerated decline in the 3 years prior to assessment.

He had been virtually confined to the house in recent years, although he still accompanied his wife shopping. He had been unable to find his way about the home and had mistaken the bedside cabinet for the lavatory on a number of occasions. His placid personality had changed and he became uncharacteristically aggressive and argumentative, using foul language at times. He had no insight into his illness until recently, when a psychiatrist informed him of his problems.

His memory for recent events had been very poor and he had developed word-finding difficulties during the year prior to assessment (October 1991). He managed to mow the lawn, but had given up gardening because the previous summer he planted vegetables in the wrong place. He was still able to sit down and look at a book, although it would frequently be upside down. He was unable to change the television channel or follow a programme. He was noted by his wife to have jerking movements in the hands and episodes when he suddenly claimed to smell smoke and then stare into space.

At the age of 48 years he had a myocardial infarction which was complicated by cardiac arrest which required defibrillation. There is no other relevant medical history. He had been a lifelong heavy smoker.

He had been investigated for memory difficulties prior to his myocardial infarction when a CT brain scan had demonstrated cerebral atrophy in excess of that expected for his age. Serum folic acid, thyroid function test and treponemal serology were normal, but the mean cell volume was a little raised at 102 femtolitres and the γ glutaryl transferase was also elevated, consistent with his daily consumption of home brewed beer. The serum vitamin B_{12} was reduced and he was commenced on replacement therapy.

On examination (A.M.K. and S.N., October 1991) he was disorientated in time and place and achieved 14 out of 30 on the Mini Mental State examination. The Clinical Dementia rating was grade 2 (moderately affected) and he had a Blessed Dementia rating of 16. There was little spontaneous speech and there were marked word-finding difficulties. Cranial nerve examination was normal including the sense of smell. His gait was slightly stooped but with normal arm swing and no other extrapyramidal signs. A pout reflex was elicited. Myoclonus was seen in the arms and legs but there was no startle myoclonus. The limbs were normal with regard to power, tone, reflexes and sensation. There was evidence of body part usage on miming, suggestive of ideomotor apraxia but he was still able to copy gestures.

On the WAIS-R he obtained a verbal IQ of 76 and a performance IQ of 66. His National Adult Reading Test (NART) IQ equivalent was 85. His scores were at chance on both the verbal and visual versions of the Recognition Memory Test. This is well below the first percentile. On the easy Oldfield Picture Naming he performed fairly competently scoring 26 out of 30. His score on the British Picture Vocabulary Scale was at the level of a 14-year-old (118 out of 150). His performances on an arithmetic test and a spelling test were both below the fifth percentile (0 out of 24; 2 out of 30, respectively). On a perceptual test his performance was rather better, with a score just above the 10th percentile (Silhouettes Test 17 out of 30). On a test of visuospatial skills he scored close to the fifth percentile (Cube Analysis 5 out of 12) and on a test of speed and attention (Cancelling A's) he performed at a very impaired level, scoring well below the first percentile. He failed the Weigl sorting task, only finding one solution. In summary, he showed a moderately severe global cognitive deterioration and a severe global memory deficit. His arithmetic skills were particularly poor. In the context of these widespread deficits he showed relatively preserved language skills.

III.15. (Age at onset 51 years.) This 58-year-old housewife's medical practitioner had 5 years earlier alerted her husband to an apparently long-standing 'communication difficulty', which had gradually worsened. Her husband had not noted anything abnormal until this time, but it is clear that there had been problems since she had to be accompanied shopping and was unable to cope with sums of money.

Her past medical history revealed that she had always had a 'useless' left arm, but it was uncertain if there had been any birth trauma to account for this. At the age of 46 years she had a right mastectomy for carcinoma of the breast.

At the age of 55 years her GP arranged admission to her local neurological centre for investigation of episodes of loss of consciousness and poor memory. Examination at this time revealed poor orientation and performance on arithmetic and proverb comprehension. A left hemiparesis was noted with hypereflexia and cortical sensory changes. A CT brain scan showed focal expansion of the right lateral ventricle. The EEG showed a slow dominant rhythm with episodes of high voltage slow activity. Thyroid function, vitamin B_{12}, serum folate and CSF examination were normal. Alzheimer's disease was diagnosed and the left hemiparesis was considered to be congenital.

Recent examination (A.M.K. and S.N., October 1991) revealed that she was severely affected with a clinical dementia rating of 3 (severe) and 0 out of 30 on the Mini Mental State examination and a score of 23 on the Blessed Scale. She had become incontinent of urine and almost everything had to be done for her, including washing, dressing and feeding, although she still attended her hairdresser. She now failed to recognize her husband and called him 'the man with glasses'. She was completely disorientated and understood few if any of our requests.

There was a left hemiparesis and sensory inattention. The tone on the left side was spastic with hyperreflexia and an extensor plantar response but no clonus. There was a left upper quadrant visual inattention and there was limitation of upgaze. She managed to cough and yawn to command but was unable to demonstrate how to clean her teeth. When given a tooth brush she was unable to use it. Myoclonic jerks were observed in her limbs. A pout reflex and left grasp reflexes was elicited.

She was untestable on formal neuropsychological assessment; she did, however, name three items on the Oldfield Picture Naming test and read 27 words on the Schonell reading test. She appeared unable to understand simple task instructions. Jargon was noted in her spontaneous speech, although this was very limited in content. Her syntax and prosody appeared to be relatively well preserved.

III.16. (Age at onset 40 years.) This 55-year-old right-handed builder presented with a 15-year history of progressive memory problems. Initially he forget appointments and became uncharacteristically short tempered. He was employed until the age of 53 years, but during much of the last 5 years at work he had difficulties with even the simplest of instructions. There was a change in his personality, with lack of confidence and depression. He was jealous of others and accused his wife of infidelity.

His workmates noted that he mislaid his tools and they had to show him to his place of work, as he was unable to remember what task he was doing from day to day. They found that he would buy a second newspaper at lunch-time, failing to remember the one he had purchased earlier in the day. He complained of low back pain which kept him off work for months at a time and focused this as his main problem.

He experienced a number of episodes lasting ~30 s in which he became rigid and pale. There were no stereotyped movements associated with these attacks. One occurred whilst he was driving and an accident was narrowly averted. For 18 months prior to assessment he was often morose and expressed suicidal thoughts. He began to experience difficulty finding words. He had little insight into his condition and spoke inappropriately about going back to work. Whilst on holiday abroad in 1991 he became lost and was separated from his wife for over 24 h until found by the police. At that time he also developed dressing difficulties.

On examination he scored 14 on the Mini Mental State examination, between 1 and 2 on the Clinical Dementia rating (mild to moderate) and 12 on the Blessed Dementia rating scale. He was disorientated in time and place and was unable to write a sentence spontaneously, although he could copy one. He had difficulty copying a drawing.

There were no abnormalities of the cranial nerves apart from a conductive deafness. There was a pout reflex and a palmar mental reflex. The gait was anatalgic due to back pain. The limbs were normal except for myoclonic jerks in both hands. He showed no ideational apraxia but executed a sequence of mimes only poorly and was unable to copy complicated hand postures. He showed ideational dysgraphia, being able to copy but not write his own name.

Thyroid function, serum vitamin B_{12}, folate, treponemal serology, copper studies, autoantibodies, including anti-cardiolipin antibody and protein electrophoresis, were normal or negative. Cerebrospinal fluid examination was normal. A resting EEG lacked an alpha rhythm and a sleep deprived EEG showed moderate disturbance of cerebral activity with no focal or epileptiform abnormalities. A magnetic resonance imaging brain scan showed diffuse cerebral cortical atrophy most marked in the parietal lobes. Positron emission tomography using [^{18}F]fluoro-deoxyglucose showed biparietal, bitemporal hypometabolism. (Fig. 3).

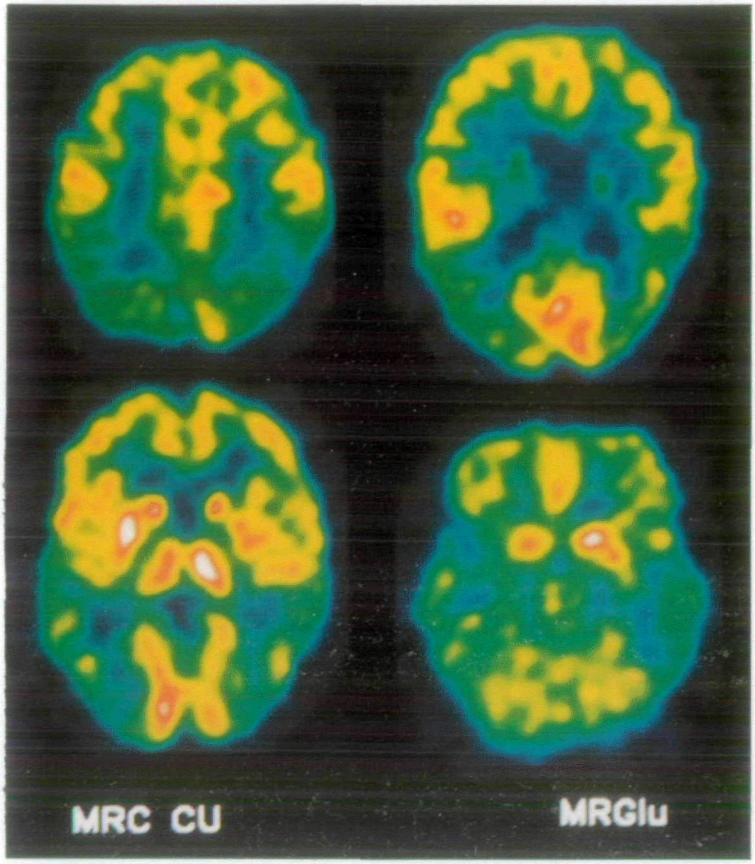

FIG. 3. Positron emission tomography scan of individual III.16. Four representative slices of an image showing the metabolic rate for glucose calculated following an injection of 5 mCi [^{18}F]fluorodeoxyglucose are shown. Striking parieto-temporal hypometabolism is seen denoted by the posterior deficit (blue/green on scale) as opposed to that in the frontal cortex (red/yellow on scale).

On the WAIS-R he obtained a Verbal IQ of 79 and a performance IQ of 76. His NART reading IQ equivalent was 86. His scores on both the verbal and visual versions of the Recognition Memory Test were below the fifth percentile. On a stringent graded naming test he obtained an average score of 14 out of 30 and 26 out of 30 on the easier Oldfield picture naming test. His British Picture Vocabulary Scale score was at the level of a 16.5-year-old (130 out of 150). He failed to score on an arithmetic test and obtained a borderline defective score of 5 out of 30 on a spelling test. His performance on a test of perception was below the fifth percentile (Silhouettes Test 12 out of 30) and on a test of visuospatial skills he scored close to the fifth percentile (Cube analysis 5 out of 12). He performed slightly better and at the 10th percentile on a test of speed and attention (Cancelling A's). he failed the Weigl Colour-form sorting task. In summary, he showed moderately severe global cognitive deterioration with memory functions particularly impaired. In the context of his poor arithmetic skills his other literacy skills were relatively well preserved. Language skills were relatively intact.