Clinicopathological features of familial Alzheimer’s disease associated with the M139V mutation in the presenilin 1 gene

Pedigree but not mutation specific age at onset provides evidence for a further genetic factor


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Summary

Sixteen affected individuals are described from two families with early onset autosomal dominant familial Alzheimer’s disease. A mutation at codon 139 in the presenilin 1 gene on chromosome 14 results in a methionine to valine substitution which cosegregates with the disease in these families. Onset of dementia was before the age of 50 years in all individuals. The ages at onset within each family were tightly clustered years. Serial MRIs showed progressive cortical atrophy with periventricular white matter change appearing 3–4 years into the disease. PET revealed parieto-temporal hypometabolism in all individuals scanned. The diagnosis of Alzheimer’s disease was confirmed with typical histopathology in one individual from each family.

Keywords: Alzheimer’s disease; familial; chromosome 14; presenilin; early onset; age at onset

Abbreviations: APOE = apolipoprotein E; APP = amyloid precursor protein; MMSE = Mini-Mental State Examination

Introduction

Alzheimer’s disease is usually a disease of the elderly, and most cases have been thought to be sporadic without a strong family history of the disease. However, pedigrees with an early age at onset (under 65 years) and a clear autosomal dominant pattern of inheritance of Alzheimer’s disease have been recognized since the 1930s.

Three separate genetic loci have now been identified at which mutations are associated with early onset familial Alzheimer’s disease and marked allelic variability has been found at these loci. The first locus found was the amyloid precursor protein (APP) gene on chromosome 21; three different point mutations at APP 717 and a double mutation at APP 670/671 cosegregate with familial Alzheimer’s disease with ages at onset from 43 to 56 years (Chartier Harlin et al., 1991; Goate et al., 1991; Murrell et al., 1991; Mullan et al., 1992). APP mutation families are, however, extremely rare

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with <20 families reported world wide, representing <2% of early onset familial Alzheimer’s disease.

The majority of cases of early onset familial Alzheimer’s disease are instead accounted for by a genetic locus which, in 1992, was mapped by linkage studies to the long arm of chromosome 14 (Schellenberg et al., 1992). This locus causes the most aggressive form of familial Alzheimer’s disease with ages at onset as early as 30 years. A novel gene, presenilin 1, on chromosome 14 has recently been identified in which mutations are pathogenic for familial Alzheimer’s disease (Alzheimer’s Disease Collaborative Group, 1995; Sherrington et al., 1995). Mutations in a further novel gene presenilin 2, encoded on chromosome 1, are also associated with early onset autosomal dominant Alzheimer’s disease (Levy-Lahad et al., 1995b; Rogas et al., 1995). These two new genes have considerable sequence homology and appear to code for membrane associated proteins with as yet undetermined physiological significance.

Considerable allelic variability is apparent in these newly identified genes with over 30 different mutations already identified (Alzheimer’s Disease Collaborative Group, 1995; Campion et al., 1995; Cruts et al., 1995; Rogas et al., 1995; Sherrington et al., 1995; Sorbi et al., 1995b; Tanahashi et al., 1995; Van Broeckhoven, 1995; Wasco et al., 1995; Boteva et al., 1996).

It is clear that in familial Alzheimer’s disease important gene to gene interactions occur. The most clearly established being the modification of the age at onset in APP families produced by apolipoprotein E (APOE) status: the APOE ε4 allele reduces the age at onset whereas the ε2 allele delays it (Sorbi et al., 1995a). However, APOE does not appear to affect age at onset in familial Alzheimer’s disease linked to chromosome 14 (Van Broeckhoven et al., 1994; Levy Lahad et al., 1995a).

Predating the discovery of genetic heterogeneity, significant phenotypic heterogeneity had been shown within the familial Alzheimer’s disease group (Bird et al., 1989). Even within the chromosome 14 linked families, studies have demonstrated heterogeneity between families with significant differences in the prevalence of clinical features such as myoclonus or seizures and perhaps more significantly in the ages at disease onset (Haltia et al., 1994; Lampe et al., 1994; Kennedy et al., 1995). The discovery of the presenilin 1 gene permits comparisons of chromosome 14 linked families with identical mutations. Kindreds with known mutations provide an ideal opportunity to examine the specificity of the phenotype and to determine the influence of epigenetic factors.

Kennedy et al. (1995) reported a chromosome 14 linked family (F148) with a consistent age at onset and a clinical profile characterized by early dyscalculia, an impairment of speech production and relative absence of anomia. They argued that the differences between this family and other chromosome 14 linked families represented allelic heterogeneity. The genetic defect in this family has now been established as a novel point mutation M139V in the presenilin 1 gene. An additional British family with early onset familial Alzheimer’s disease has been found to carry an identical mutation (Alzheimer’s Disease Collaborative Group, 1995). We present and compare the clinicopathological and neuropsychological features of these two pedigrees which, between them, include 16 affected family members spanning four generations.

**Methods**

Prior to the description of genetic linkage to chromosome 14, affected and ‘at risk’ individuals from pedigrees with early onset familial Alzheimer’s disease were recruited to take part in a longitudinal clinical, neuropsychological and neuroimaging study. Ethical approval for this study was obtained from the local ethics committee and subjects gave informed consent to participate. Following the discovery of the presenilin 1 gene, these pedigrees were screened for mutations and two large families carrying the same M139V substitution were identified. Age at onset, first symptoms, clinical progression, duration of illness and age at 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. Details of deceased individuals were obtained by interview with relatives and from hospital case notes. All living affected family members were assessed clinically and where possible underwent neuropsychological assessment, MRI and PET scanning. The technical details of the MRI and PET scanning procedures have been reported previously (Kennedy et al., 1995). PET data were analysed using statistical parametric mapping to determine the distribution of hypometabolism for individual subjects compared with normal controls (Kennedy et al., 1995). MR imaging included axial dual-echo (T2- and proton density-weighted) sequences and volumetric coronal T1-weighted gradient echo scans. One subject from each family (F148: 2.4 and F206: 3.8) was scanned approximately annually, generating a total of five scans each. Other subjects had a single MR scan when first assessed. The MRI films were assessed by a neuroradiologist blind to the individual diagnoses and clinical details.

The Medical Research Council guidelines for assessment of research patients with Alzheimer’s disease provided the basis for the clinical interview which also included the Mini-Mental State Examination (MMSE) and the Clinical Dementia Rating (Folstein et al., 1975; Hughes et al., 1982; Medical Research Council, 1986). Psychiatric symptoms were not assessed formally. The history was verified by independent interview with the spouse or other close relative. APOE genotyping was performed on affected individuals where a blood sample was available, in one further deceased individual (Case 3.1 in F206) it was possible to deduce the APOE genotype from the APOE status of first degree relatives.

**Results**

**Overview**

The kindreds, F148 and F206, are of British origin and do not appear to be related. Figures 1 and 2 show the family
Early onset familial Alzheimer’s disease due to the M139V mutation

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trees. F148 comprises seven affected individuals in two generations; some clinical details of this family have previously been reported (Kennedy et al., 1995). F206 includes nine affected individuals spanning four generations. Detailed case histories for F206 are given in the Appendix. Affected individuals included smokers and non-smokers and none had used illicit drugs or excessive alcohol. Two individuals (F148, Cases 2.3 and 2.6) had sustained head injuries with loss of consciousness, 18 and 5 years, respectively, before the onset of dementia. There was no other significant medical history in any individual.

**Age at onset**

Ages at onset for those individuals for whom reliable details were available (13 out of 16) are shown in Table 1. There was no overlap in the ages at onset in the two families with the range in F148 being 42–48 years (mean 44.3, median 43 years) and the range in F206 was 36–40 years (mean 37.7, median 38 years). The ages at onset in F148 were significantly higher than in F206 ($P < 0.005$, Mann–Whitney two-tailed $U$ test). This difference in age at onset could not be accounted for by APOE status (Table 1).

Similarly, the ages at death (49–52 years) in the F148 family were later than in the F206 family (42–49 years). Furthermore, the three living affected F148 members were all already in their mid to late fifties. This contrasts with the mean age at death in F206 of 45 years with no affected family member having lived beyond 49 years of age. The duration of illness of the deceased members of the two families was not significantly different, ranging from 6 to 10 years.

**Clinical presentation and neurological features**

Memory impairment, first noticed by other family members, was the earliest symptom in all but one of the affected subjects. Neurological examination was unremarkable in the early stages, problems with praxis and visual disorientation appeared in moderately affected subjects. Myoclonic-like jerks, initially of the fingers, were common in both families. Where it was possible to date the onset of myoclonus, it was noted within 3–6 years of the onset of symptoms. Seizures were also common, particularly in F206 where all severely affected individuals developed generalized seizures (see Table 1 and Appendix).

**Neuropsychology**

The neuropsychological results from six individuals studied in detail, three from each family, are given in Tables 2A and 2B.

**Intellectual function**

A shortened version of the Wechsler Adult Intelligence Scale Revised (Wechsler, 1981) was administered and a full-scale IQ pro-rated from four verbal subtests and three performance subtests. The National Adult Reading Test was administered to obtain a Reading IQ equivalent score which gives an estimate of the individual’s optimum level (Nelson, 1991). The discrepancy between these scores provides a measure of the severity of intellectual deterioration. A significant decrement in the current level of functioning was already present at the initial assessment in all subjects except Case 2.4 (F148) and Case 3.10 (F206); by the second assessment it was seen in all subjects.

**Memory skills**

At presentation only one individual, Case 3.10, had both verbal and visual memory functions above the 5th percentile.
Table 1  Clinical features of affected individuals for the two families

<table>
<thead>
<tr>
<th>APOE genotype</th>
<th>Age at onset (years)</th>
<th>Age at death (years)</th>
<th>Present age (years)</th>
<th>Duration of illness (years)</th>
<th>First symptom</th>
<th>Preserved insight</th>
<th>Presence of myoclonus (age)</th>
<th>Presence of seizures (age)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F148</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2</td>
<td>44</td>
<td>47</td>
<td>NK</td>
<td>7</td>
<td>Memory</td>
<td>NK</td>
<td>NK</td>
<td>NK</td>
</tr>
<tr>
<td>2.1</td>
<td>3.4</td>
<td>55</td>
<td>10</td>
<td>Memory</td>
<td>NK</td>
<td>NK</td>
<td>+ (&lt;48)</td>
<td>+</td>
</tr>
<tr>
<td>2.3</td>
<td>42</td>
<td>7</td>
<td></td>
<td>Memory</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.4</td>
<td>3.4</td>
<td>59</td>
<td>&gt;10</td>
<td>Memory</td>
<td>+ (&lt;54)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5</td>
<td>3.3</td>
<td>55</td>
<td>&gt;11</td>
<td>Personality</td>
<td>+ (&lt;49)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.6</td>
<td>3.4</td>
<td>55</td>
<td>&gt;9</td>
<td>Memory</td>
<td>+ (&lt;50)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F206</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.3</td>
<td>3.6</td>
<td>43</td>
<td>7</td>
<td>Memory</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.1</td>
<td>2.3†</td>
<td>40</td>
<td>9</td>
<td>NK</td>
<td>–</td>
<td></td>
<td>+ (&lt;47)</td>
<td>+</td>
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<tr>
<td>3.2</td>
<td>39</td>
<td>6</td>
<td></td>
<td>Memory</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.5</td>
<td>3.4</td>
<td>42</td>
<td>&gt;7</td>
<td>Memory</td>
<td>+ (42)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.8</td>
<td>3.3</td>
<td>47</td>
<td></td>
<td>Memory</td>
<td>+ (41)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.10</td>
<td>3.3</td>
<td>41‡</td>
<td>NT</td>
<td>Memory</td>
<td>+ (41)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.1</td>
<td>3.3</td>
<td>42</td>
<td>&gt;5</td>
<td>Memory</td>
<td>+ (40)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In the last three columns +/- indicate presence/absence of insight, myoclonus or seizures, respectively; in last two columns (age) = age (in years) at which myoclonus/seizures first noted. NK = not known. *This subject died of TB and therefore his age at death is not directly comparable. † This subject's APOE status was deduced from the results of family members. ‡ This subject died of meningitis and therefore his age at death is not directly comparable.

Table 2A  Neuropsychological test scores in individuals from family 148

<table>
<thead>
<tr>
<th>Test</th>
<th>F148 individual</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.4</td>
</tr>
<tr>
<td>NART IQ</td>
<td>116</td>
</tr>
<tr>
<td>WAIS-R FSIQ</td>
<td>105</td>
</tr>
<tr>
<td>Recognition memory: words (max 50)†</td>
<td>37**</td>
</tr>
<tr>
<td>Recognition memory: faces (max 50)‡</td>
<td>26**</td>
</tr>
<tr>
<td>Naming (max 30)</td>
<td>25</td>
</tr>
<tr>
<td>Arithmetic (max 24)</td>
<td>21</td>
</tr>
<tr>
<td>Object perception (max 30)</td>
<td>21</td>
</tr>
<tr>
<td>Space perception (max 10)</td>
<td>10</td>
</tr>
</tbody>
</table>

WAIS-R = Wechsler Adult Intelligence Scale Revised (Wechsler, 1981); FSIQ = full-scale IQ pro-rated from four verbal subtests and three performance subtests; NART = National Adult Reading Test. NT = not tested. *≈5th percentile; **≈1st percentile. † Shortened version of recognition memory test was used when patients performed at chance on the long version; the maximum score was then 25 as indicated.

Table 2B  Neuropsychological test scores in individuals from family 206

<table>
<thead>
<tr>
<th>Test</th>
<th>F206 individual</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4.1</td>
</tr>
<tr>
<td>NART IQ</td>
<td>NT</td>
</tr>
<tr>
<td>WAIS-R FSIQ</td>
<td>76**</td>
</tr>
<tr>
<td>Recognition memory: words (max 50)†</td>
<td>30**</td>
</tr>
<tr>
<td>Recognition memory: faces (max 50)‡</td>
<td>30**</td>
</tr>
<tr>
<td>Naming (max 30)</td>
<td>14</td>
</tr>
<tr>
<td>Arithmetic (max 24)</td>
<td>2**</td>
</tr>
<tr>
<td>Object perception (max 30)</td>
<td>18</td>
</tr>
<tr>
<td>Space perception (max 10)</td>
<td>5</td>
</tr>
</tbody>
</table>

See Table 2A footnote for details.
as assessed by the Recognition Memory Test (Warrington, 1984). One individual from each family initially had a selective verbal deficit, the others had both verbal and visual memory impairments at their initial assessment. In all subjects, the memory deficits progressed with all memory scores falling below the 1st percentile at later assessments.

**Verbal skills**

Naming, assessed on the Graded Naming Test (McKenna and Warrington, 1983), was strikingly preserved in all individuals tested in both families, and was still within the normal range (>25th percentile) even in the presence of significant cognitive impairment.

A speech production deficit was a prominent feature at an early stage in the disease progression in two individuals of F148 who were studied in detail. It should be noted that in the original description of this family only two individuals had a speech production deficit; the third affected individual has subsequently developed a similar deficit. These deficits were documented objectively on tests of repetition and reading.

**Calculation skills**

These were assessed on the Graded Arithmetic Test (Jackson and Warrington, 1986). In contrast to performance on the naming test, all but two of the individuals were already impaired on the arithmetic test at their initial assessment. In the other two individuals, one from each family, their performance declined on subsequent testing.

**Perceptual skills**

Object and space perception were assessed on two subtests of the Visual Object and Space Perception Battery (Warrington and James, 1991); the Object Silhouettes and Cube Analysis Test respectively. Overall, impairments of space perception were observed earlier than impairments of object perception in individuals from both families (Tables 2A and 2B).

**Neuroimaging: MRI**

**Family F148**

The initial scan of Case 2.4 showed only mild diffuse atrophy; the next four scans showed progressive atrophy, with the appearance of diffuse periventricular white matter signal change and small peripheral white matter lesions. The scans of Cases 2.5 and 2.6 showed generalized cerebral atrophy, and confluent periventricular white matter change was present in Case 2.6.

**Family F206**

In the initial MRI scan of Case 3.8 the only abnormal feature noted was signal change in the hippocampi. However, by the time of the third scan atrophy was obvious, particularly in the parietal lobes. This atrophy increased markedly over the next two scans and additionally, diffuse white matter signal change appeared in these later scans. Only mild sulcal widening and scattered white matter lesions were noted in the MR scan of Case 3.10.

**Neuroimaging: PET**

$^{[18}F]^{\text{Fluorodeoxyglucose}}$ PET was utilized to calculate regional cerebral glucose metabolism. Scans were performed on the three living affected members of F148 (2.4, 2.5 and 2.6) and Case 3.8 of F206. Cases 2.5 and 2.6 (F148) and Case 3.8 (F206) had a similar symmetrical pattern of posterior parieto-temporal hypometabolism with additional frontal hypometabolism more apparent on the left. In Case 2.4 (F148) hypometabolism was more focal with an asymmetrical left temporal deficit and no frontal changes.

**Neuropathology**

Post-mortem examinations were conducted on one individual from each family and in both cases confirmed the diagnosis of Alzheimer’s disease. In F206, the examination was on Case 3.5: the brain weighed 1080 g after fixation and showed diffuse atrophy with relative preservation of the occipital lobes. Coronal slicing revealed enlarged lateral ventricles with widening of their angles. The sulci were widened and the gyri narrowed. The basal ganglia and cerebellum were normal. There was no evidence of any focal pathology. The histological appearance was typical for severe Alzheimer’s disease with abundant senile plaques, neurofibrillary tangles and neuropil threads throughout the cerebral cortex (Fig. 3A); quantitative analysis fulfilled all criteria for Alzheimer’s disease. The hippocampus showed many tangles, neuritic plaques (Fig. 3B) and granulo-vacuoles and a few Hirano bodies. The substantia nigra and locus coeruleus displayed neuronal loss, extra-neuronal pigment, a few tangles, but no Lewy bodies (Fig. 3C). Amyloid angiopathy was shown to be present with the vascular walls staining positively with an antibody to $\beta\text{A4}$ protein. Immunocytochemistry for $\beta\text{A4}$ also showed positive staining of senile plaques and various types of diffuse deposits (Fig. 3D). There were no Lewy bodies in the cerebral cortex. Case 2.1 (F148), described by Kennedy et al. (1995), also had histological features of severe Alzheimer’s disease with large numbers of senile plaques and neurofibrillary tangles throughout the cerebral cortex.

**Discussion**

The individuals in these two pedigrees display several similarities in their patterns of clinical progression. Myoclonic jerks appeared commonly and at a relatively early stage in the illness (<5 years from first symptoms). Some studies in sporadic Alzheimer’s disease have suggested that both
myoclonus and seizures reflect disease severity (Hauser et al., 1986; Chen et al., 1991). By contrast, in several chromosome 14 linked pedigrees myoclonus has been noted to be an early feature (Feldman et al., 1963; Frommelt et al., 1991; Martin et al., 1991; Haltia et al., 1994; Lampe et al., 1994). Lampe et al. (1994) reported that in family L (chromosome 14 linked) the onset of myoclonus occurred >3 years before death, at about the midpoint of the total disease course. This is consistent with our findings of an onset of myoclonus as early as 3 years from first symptoms (range 3–6 years). A high incidence of early myoclonus appears to be characteristic of the phenotype of this mutation. Mayeux et al. (1985) noted that patients with myoclonus were younger at onset and our findings may partly reflect the young age of these individuals rather than be specific to this new mutation.

Generalized seizures were extremely common, particularly in those individuals with the earliest age at onset. Frommelt et al. (1991) also found an increased prevalence of seizures

Fig. 3 Neuropathology from Case 3.5. (A) Neuropil threads are abundant in addition to tangles in the temporal neocortex. Modified Bielschowsky. (B) Many neuritic plaques and neurofibrillary tangles are present in the hippocampus. Modified Bielschowsky. (C) Neurofibrillary tangle and extraneuronal pigment in the substantia nigra. (D) β-Amyloid in the form of plaques, diffuse and punctate deposits in the frontal lobe. Immunoperoxidase, ABC method. Bar = 50 µm
in their familial Alzheimer’s disease cases, particularly in those patients with myoclonic jerks. Lampe et al. (1994) reported seizures and myoclonus occurring at roughly the same point in the disease course. In all but one of our cases, myoclonus predated seizures. Generalized seizures occurring up to 3 years before death, and 1–3 years after myoclonus appears, would seem to be characteristic of this mutation.

The neuropathology of the affected individuals in the two families was similar to each other and to other cases of familial or sporadic Alzheimer’s disease. This observation is in line with results of a quantitative analysis which did not reveal significant differences in βA4 protein deposition in the hippocampus and the neocortex between familial Alzheimer’s disease and the sporadic form of the disease (Cairns et al., 1993). Moreover, cases of familial Alzheimer’s disease and sporadic Alzheimer’s disease have been shown with immunohistochemistry and Western blotting to have the same cytoskeletal pathology (Lantos et al., 1992).

Our MRI findings were similar to studies of sporadic Alzheimer’s disease (Fox et al., 1995) and support the view that, while atrophy is a characteristic feature in moderately affected Alzheimer’s disease subjects, in mild cases scans may appear within the normal range. The longitudinal MR assessments in this study suggest that white matter changes, usually periventricular, appear during the course of the illness. White matter change on MRI has been found to be more frequent and more extensive in Alzheimer’s disease cases than in controls (Schmidt, 1992; Fox et al., 1995). However, studies excluding subjects with vascular risk factors have not shown any significant difference between patients with Alzheimer’s disease and elderly controls (Leys et al., 1990). Our cases were young and essentially free of vascular risk factors, suggesting that the observed white matter changes are due to the Alzheimer’s disease process.

The PET findings were similar to those in sporadic Alzheimer’s disease with metabolism particularly reduced in the temporal and parietal cortices (Frackowiak et al., 1981; Haxby et al., 1987). Left sided deficits were more severe in two subjects and were confined to the left parietotemporal region at initial scan (in the two least affected); this is in agreement with previous PET data showing left hemisphere asymmetry (Duara et al., 1986; Lowenstein et al., 1989).

The neuropsychological profiles of the individuals studied in detail were similar and some similarities spanned both pedigrees. The presentation of memory impairment with steady progression to more generalized cognitive deficits seen in these subjects is common to both familial Alzheimer’s disease and sporadic Alzheimer’s disease (St George-Hyslop et al., 1989; Rossor, 1992). In those individuals tested early enough, verbal memory loss preceded visual memory problems. Early selective loss of verbal memory was previously reported in a longitudinal study of a single chromosome 14 linked familial Alzheimer’s disease case whose assessments included the period of earliest symptoms (Newman et al., 1994). By contrast selective visual memory loss in early onset familial Alzheimer’s disease has not, to our knowledge, been reported.

Arithmetic skills declined ahead of other literacy skills and was an early feature in two. Acalculia has previously been reported in some affected individuals from large Alzheimer’s disease pedigrees (Nee et al., 1983) including both chromosome 14 linked and APP 717 families (Karlinsky et al., 1991; Kennedy et al., 1993). By contrast, there was marked and surprising preservation of naming at a stage when intellectual decline was already profound and memory had been affected for several years.

The unusual finding of an impairment of speech production characterized by stammering in propositional speech was seen in all three living affected members of F148. Kennedy et al. (1995) suggested that such specific phenotypic differences between families implied allelic heterogeneity. While allelic heterogeneity has been confirmed, this particular defect has not been reproduced in another family (F206) with the same pathogenic mutation. Thus a consistent phenotype is seen within a family but not necessarily between families with the identical mutation.

The most important phenotypic difference between the two families was the significantly earlier age at disease onset in F206. Age at onset in familial Alzheimer’s disease has been considered to be largely determined by the underlying genetic defect (van Duijn et al., 1991). These two families have ages at onset which fall within the range of onset reported for chromosome 14 linked pedigrees and are both younger than the age at onset found in the APP mutation families (Chartier-Harlin et al., 1991; Goate et al., 1991; Karlinsky et al., 1992; Mullan et al., 1993). Allelic heterogeneity has been proposed to explain the observed differences in age at onset in chromosome 14 linked families. However, despite identical mutations, these two pedigrees have very significant differences in their ages at onset. F206 has a tightly grouped age at onset around 38 years with all affected individuals symptomatic by the age of 40 years. By contrast, the mean age at onset of individuals in F148 is 44 years with the youngest age at onset being 42 years. Accurate determination of age at onset is notoriously difficult as it often depends on the observations and recollections of family members. The knowledge that previous generations had become affected at a particular age may introduce bias with symptoms being ‘looked for’ by family members. However, it is unlikely that such observer error could account for the difference of over six years in age at onset between these two families. In addition several individuals in each family were assessed when only mildly affected when onset may more accurately be determined. Age at death is less susceptible to recollection bias, but may be influenced by coincident pathology and by the level of care provided. Nonetheless, the ages at death also support a major phenotypic difference between the two families; no affected individual in F206 had survived beyond the age of 49 years, while all three living affected members of F148 were already in their mid to late fifties. In F148, only one affected individual,
Case 1.2, died before the age of 49 years, and his age of death is not directly comparable as he died of pulmonary tuberculosis when only moderately affected by Alzheimer’s disease. These differences in ages at onset and death could not be explained by differences in a history of head injury or smoking. One potential genetic explanation that was considered for this difference was APOE status. The APOE ε4 allele is associated with earlier age at onset in sporadic Alzheimer’s disease and in the APP mutation families (Corder et al., 1993; Poirier et al., 1993; Locke et al., 1995; Sorbi et al., 1995a). By contrast, the results from these two families confirm a lack of influence of APOE on age at onset in familial Alzheimer’s disease associated with presenilin 1 mutations (Van Broeckhoven et al., 1994). Specifically there was no evidence to suggest that the ε4 allele was associated with a lower age at onset, and the differences in age at onset between the two families was just as evident when family members with the same APOE status were compared (Table 1). The significant difference in age at onset between these two families implies that, with the presenilin 1 mutation disease, age at onset is under the influence of a further factor. We suggest that the tight age at onset within each family, across several generations, is evidence that this further factor is genetic. This genetic factor is not APOE but may have analogous risk-modifying effects.

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References


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Appendix
Case histories from Family 206
Cases 1.1 and 2.1 both died in their fortiess following a dementing illness.

Case 2.3
Age at onset, 36 years; age at death, 43 years. This right-handed woman started to mislay items and became increasingly forgetful at the age of 38 years. Her social skills were preserved and she had considerable insight into her difficulties. At the age of 39 years she was admitted to a local hospital for investigation. The routine examination was normal, although she performed poorly on cognitive tests. An air encephalogram showed evidence of cortical atrophy. Routine blood and CSF examination were normal. At the age of 42 years she was readmitted unable to cope at home. There was no propositional speech but she continued to answer simple questions correctly with yes/no answers. ‘Twitching movements’ in all limbs were documented. An EEG only showed decreased alpha activity. She had numerous generalized seizures and died aged 43 years from bronchopneumonia and a urinary tract infection.

Case 3.1
Age at onset, 40 years; age at death, 49 years. At the age of 41 years this right-handed miner got lost when visiting his wife in hospital. In the preceding year he was thought to have been more forgetful and ‘was not quite right’. He denied anything was wrong with him and had to be forced to see a doctor. At this stage he could not be relied upon to remember even simple shopping lists and made errors in making a cup of coffee. He continued to ride a motorbike until he had a serious accident driving into the back of a car. He complained then of being unable to see properly though he had a normal assessment by an optician. He was admitted for long-term care aged 45 years. Two years after his admission, aged 47 years, he had a generalized seizure; seizures remained frequent until his death aged 49 years.

Case 3.2
Age at onset, 39 years; age at death, 46 years. This right-handed woman became increasingly forgetful from the age of 39 years and this affected her ability to perform tasks at work. She developed difficulty in walking and started to descend the stairs on her buttocks. She was unsteady and tended to topple over if she bent to tie her shoe laces but was able to walk if accompanied. She had increasing word-finding difficulties. She had a number of generalized seizures and was also noted to have ‘jerky’ movements. She was admitted for debridement of decubitus ulcers shortly before her death.

Case 3.5
Age at onset, 36 years; age at death, 42 years. This left-handed man was an NCO in the Army. Progressive cognitive decline was noted from the age of 36 years. He became forgetful, mislaid things and brought back the wrong items if sent on an errand. He became uninterested in his work, spending much of the day in bed, resulting in his dismissal from his job because of poor attendance. At the age of 37 years he could no longer orientate himself when driving and had developed word-finding difficulties. He started to wander and was referred for investigation. The general examination was recorded as normal. Psychometric testing demonstrated a marked memory deficit with mild generalized intellectual impairment. A CT scan showed mild cerebral atrophy. All other investigations were normal. A diagnosis of ‘presenile dementia’ was made and he was advised not to drive. He had relatively little insight into his cognitive difficulties. At the age of 41 years myoclonic jerks were observed and he had several generalized seizures. Pout, rooting, palmo-mental and grasp reflexes were elicitable and cogwheel rigidity observed, although at this stage he was receiving phenothiazine medication. He walked with an apractic gait and...
could not manage tests of limb apraxia. Post-mortem examination confirmed the diagnosis of Alzheimer’s disease (Fig. 3).

Case 3.8
Age at onset, 39 years; current duration 7 years. This right-handed woman developed cognitive difficulties at the age of 39 years. She was aware of her symptoms and gave a history of recent forgetfulness with difficulty remembering shopping lists and taking telephone messages. Her speech and orientation were unaffected and her social skills remained intact. The following year, a CT scan showed prominent sulci but no other abnormality. At the age of 42 years she scored 20/30 on the MMSE and 0.5 on the Clinical Dementia Rating. Her main complaints were still of memory, but she also had minor word-finding problems and difficulty making decisions. Neurological examination was normal, apart from myoclonic jerks in her fingers. Investigations were normal apart from an EEG which showed mild generalized slowing and serial MRI scans which showed progressive atrophy. She developed progressive impairment of word-finding and praxis, although she maintained an appropriate social facade. Six years after the onset of the illness she started to need help with dressing and toileting and had difficulty using a knife and fork and finding her way around and was occasionally unsure of her way within the house. She had also been noticed to walk into objects, such as door frames, apparently without having seen them. Her husband felt that she also had difficulty seeing objects such as the telephone. Conversation was difficult and sentences were often unfinished. Myoclonus was very common, particularly in the mornings and was violent enough to result in crockery being knocked across the room. Her MMSE score had fallen to 6/30. On examination, tone and reflexes were normal, myoclonus was prominent, praxis was very impaired and visual disorientation was present.

Case 3.10
Age at onset, 38 years; age at death, 41 years This 40-year-old right-handed man was made redundant from a manual job when he was aged 37 years. Over the following year, his wife and children noticed he had difficulty finding items which he had just put down such as his keys or cigarettes and was generally more forgetful. He developed ‘more of a temper’. He was slower and less confident in filling in forms and made mistakes in operating the video recorder. Aged 39 years he scored 19/30 on the MMSE with poor recall and difficulty in copying designs. He was tremulous, had finger myoclonus and had problems copying hand gestures, particularly with his left hand. There were no other focal signs. Routine investigations were normal apart from a paucity of alpha rhythm on his EEG. The MRI scan showed sulcal widening with a few scattered non-specific white matter lesions. Over the following year he deteriorated rapidly; his speech became limited and incomprehensible, he was disoriented in place and time and only recognised close family members. He was admitted to his local hospital, with a presumptive diagnosis of meningitis after becoming acutely unwell and confused, with recurrent generalized seizures. He died shortly after admission; an autopsy was not performed.

Case 4.1
Age at onset, 36 years; current duration, 6 years. Aged 36 years, this right-handed woman started having problems with her memory, losing everyday items, and duplicating purchases when shopping, although she denied memory or cognitive problems. Shortly after this she got lost whilst on holiday. Over the next 2 years her speech became increasingly repetitive, asking the same question after a few minutes. Her cognitive abilities declined and by the age of 39 years she was usually disoriented in time and occasionally in place. She complained of trouble seeing things saying there were ‘lines’ across her vision, as if looking through a blind. Her practical abilities declined rapidly over the subsequent 2 years and she was noted to have ‘jerking movements’. She was admitted to long-term care aged 40 years. Aged 41 years she had a generalized seizure, startle myoclonus had become prominent and she had become virtually bed bound and could do little for herself.