# Chromosome 14 linked familial Alzheimer's disease A clinico-pathological study of a single pedigree

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## **Summary**

*The clinical features of three affected members of a British pedigree with familial Alzheimer's diseuse are presented. This pedigree is one of six included in an earlier study which demonstrated linkage to chromosome 14. The individuals were investigated clinically and neuropsychologically, using both PET and MRI over a 4-year period. Further information from three deceased individuals was obtained, including histopathological confirmation of Alzheimer's disease in one case which came to autopsy. The mean age at onset for this family was 43 years. Neurological examination revealed myoclonic jerks in all cases, and one patient was documented to have seizures. Strikingly similar neuropsychological profiles were observed, characterized by an initial memory deficit with early dyscalculia and an impairment in speech production with relative absence of anomia. All individuals*

*showed mild degrees of cerebral atrophy and two individuals had periventricular white matter lesions. PET scanning using [ l8F]fluorodeoxyglucose showed parieto-temporal hypometabolism in all cases and the two severely affected patients with speech production changes had additional left-sided frontal hypometabolism involving Broca's area. The least affected case initially had a more asymmetrical reduction in metabolism in the left inferior temporal and supramarginal gyri; a follow-up scan showed that this deficit had become bilateral and more severe. These clinical and neuroimaging features have not been previously reported in chromosome 14 linked pedigrees; the phenotypic variability between families suggests allelic heterogeneity at the chromosome 14 locus.*

Keywords: familial Alzheimer's disease; PET; cerebral metabolic rate for glucose (CMRglu); chromosome 14; speech production deficit

# **Introduction**

Since the original descriptions of familial Alzheimer's disease (Schottky, 1932; Lowenberg and Waggoner, 1934) a large number of autosomal dominant pedigrees have been reported (Nee *et at.,* 1983; St George-Hyslop *et ai,* 1987; Sadovnick *et al.,* 1988). Various clinical features have been observed including an early age at onset, myoclonus and seizures. Molecular genetic studies have demonstrated three point

mutations on chromosome 21 at codon 717 of the amyloid precursor protein (APP) which co-segregate with the affected individuals in several familial Alzheimer's disease families (Chartier Harlin et al., 1991; Goate et al., 1991; Murrell et al., 1991). In addition a double mutation at APP  $_{670/671}$  in a Swedish family has also been reported (Mullan *et al.,* 1992a). Schellenberg *et al.* (1992) have found linkage to markers on

the long arm of chromosome 14, which has been confirmed by three other groups in North American, Belgian and British pedigrees (Mullan *et al.,* 1992b; St George-Hyslop *etal.,* 1992; Van Broeckhoven *etal.,* 1992). Linkage to chromosome 19 in later onset pedigrees has been demonstrated (Pericak-Vance *etal.,* 1991) and more recently an association with the E4allele of apolipoprotein E on chromosome 19 in these families has been described (Saunders et al., 1993; Strittmatter et al., 1993).

Despite obvious differences in age at onset, there has been little evidence to suggest that familial Alzheimer's disease is clinically, neuropsychologically, pathologically or metabolically distinct from sporadic Alzheimer's disease (Nee *et al.,* 1983; Fitch *et al.,* 1988; Grady *et al.,* 1988; Adams et al., 1989; Haupt et al., 1992). However, aphasia, myoclonus and seizures have been prominent in familial Alzheimer's disease, although it has been difficult to identify which features are due to the early age at onset and which are due to the autosomal dominant trait. Bird *et al.* (1989) examined 180 individuals from 24 kindreds with autosomal dominant familial Alzheimer's disease and described five distinct groups suggesting phenotypic heterogeneity. Two groups were distinguished by age at onset; a younger mean age at onset of 42 years and an older mean age at onset of 68 years. Myoclonus, seizures and language deficits were more common in the younger onset group. Four other groups were differentiated on the basis of clinical and pathological features.

The clinical features of APP mutation families are largely similar to those described in other familial Alzheimer's disease pedigrees with a mean age at onset which ranges from 43 to 56 years. Myoclonus and seizures have been observed in some but not all of these families (Van Duijn *et al.,* 1991a; Karlinsky *et al.,* 1992; Kennedy *et al.,* 1993), as has the preservation of naming skills. The published pedigrees with chromosome 14 linked familial Alzheimer's disease do not identify specific phenotypes, although the ages at onset appear to be younger than the APP families (Mullan *etal.,* 1993).

PET has been used to study cerebral metabolism in individuals with familial Alzheimer's disease (Cutler *et al.,* 1985; Polinsky *et al.,* 1987; McGeer *et al.,* 1990) and all cases studied to date have a parieto-temporal deficit which is also felt to be characteristic of sporadic Alzheimer's disease (Frackowiak *et al.,* 1981; Duara *et al.,* 1986). However, there have been no attempts to determine the change in metabolic profiles in individuals who share a common aetiology. We describe the neuropsychological and metabolic profiles from three affected and one unaffected individual, studied longitudinally over a 4-year period from a histologically proven familial Alzheimer's disease pedigree with chromosome 14 linkage and compare these features with other APP and chromosome 14 pedigrees.

### Pedigree overview

This British kindred is called Family 148 (F148) and has a total of seven affected individuals spanning two generations



**Fig.** 1 Family tree. Squares = males; circles = females; filled  $symbols = affected; diagonal line = decreased subject.$ 

*{see* Fig. 1). No detailed information is available about the parents of Cases I.I and 1.2, who died young and were thought to be unaffected. Detailed information is available on deceased Cases II.1 and II.3, and histopathological confirmation of Alzheimer's disease is provided for Case II. 1. Cases II.4, II.5 and II.6, who are the living affected, all fulfil NINCDS criteria for probable Alzheimer's disease (McKhann *et al.,* 1984) and were enrolled in this study prior to the description of genetic linkage to chromosome 14 (Mullan *et al., \992b).* Cases II.5 and II.6 are non-identical twins. Case II.2 was the only living unaffected sibling from generation II and was assessed as a control subject.

# Methods and results *Clinical*

Age at onset was defined as the age estimated from the reports of family members and hospital records when an individual first demonstrated signs of memory loss or personality change. The Medical Research Council (MRC) 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 (CDR) (Folstein *et al.,* 1975; Hughes *et al.,* 1982; Medical Research Council, 1986). The history was verified by an independent interview with the spouse, except for Case II.6 for whom her elder brother (Case 11.2) provided the information. The timing of each neurological assessment (A.K.) and the CDR and MMSE scores are illustrated in Fig. 2. PET and neuropsychological assessments were performed longitudinally as indicated in Fig. 2. An EEG and an MRI scan were performed at the time of the first assessment as were routine haematological and biochemical tests. In addition, Case II.4 had MRI scans at each subsequent assessment. Detailed case histories for each case are found in Appendix 1. Ethical approval for this study was obtained from the local ethics committee and patients gave informed consent to participate. The mean age at disease onset in this family is 43.3 years ( $SD \pm 2.5$  years, range 40-48 years). The duration of disease ranges from 4 to 10 years.

All three individuals presented with memory difficulties, although personality change predated the cognitive symptoms in Case II.5. In all cases, awareness of memory difficulties was preserved. Visuospatial symptoms tended to be mild at an early stage of the illness as subjects continued to drive



Fig. 2 Clinical details and time of assessment for subjects studied. This figure shows time in years horizontally. The horizontal bars represent the duration of symptoms for each of the three living individuals. Age at onset is displayed at the left hand end of the bar. The study was analysed until December 1992. The time of each neuropsychological assessment is denoted by the open circles, whereas each PET assessment is shown by the the open squares and MRI by the filled circle. The relevant MMSE and CDR values for each assessment are shown in the two rows below the appropriate symbol.

and find their way about without difficulty. Cases II.5 and II.6 were noted to develop speech problems and stammering during the illness, although this was not as evident in Case II.4. No patient was on medication, used excessive alcohol or illicit drugs. The neurological examination was largely unremarkable; however, myoclonic jerks were observed in the fingers of all three affected cases and possibly in one other deceased individual (II.1). Apraxia was a later manifestation. Case II.4 with the later age at onset was the only individual not to have had a prior significant head injury *(see* Case histories in Appendix 1). Case II.4 was found to have positive oligoclonal bands without symptoms or signs of demyelination. Thorough investigation including sensory and visual evoked potentials were normal and the lesions on MRI did not enhance with gadolinium. The clinical diagnosis remained that of familial Alzheimer's disease.

Routine haematological and biochemical tests were normal or negative including serum Vitamin B12, folate, thyroid function tests, treponemal serology and auto-antibody screening.

## *Neuropsychology*

The details of the neuropsychological tests are given in Appendix 2. Formal tests of speech production were also given to each patient on September 10, 1991 and to Case 11.6 on subsequent occasions. The first assessment of Case II.6 and the third of Case II.5 were somewhat briefer.

# *General intellectual function*

A shortened version of the Wechlser Adult Intelligence Scale-Revised (WAIS-R) (Wechlser, 1981) was administered and verbal and performance IQ measures were obtained by prorating seven subtest scores. The IQ measures together with the age scaled scores for each patient at each assessment are given in Table I. The performance of Case 11.4 on the first and second assessment was largely in keeping with his estimated high average optimal level of functioning. It was only on the third test occasion that he showed evidence of cognitive decline.

	Case $11.4$		Case 11.5			Case $11.6$							
	Assessments												
	l st	2nd	3rd	l st	2nd	3rd	l st	2nd	3rd				
Verbal IQ	112	112	108	92	72	68	94	80	76				
Performance IQ	108	107	89	94	67	NT	89	74	65				
Scaled score													
Digit span	13	13	11	8	5	3	8	6	5				
Vocabulary	12	12	13	10	6		12	9					
Arithmetic	13	12	11	9	4	2		4	4				
<b>Similarities</b>	10	$\mathbf{11}$	12	10	5	3	8	7					
Picture completion	10	10	8	11	4	<b>NT</b>	11	5	8				
Picture Arrangement	13	13	10	9	3	NT	7						
<b>Block Design</b>	11	8	8	9	4	NT	6	8					

Table 1 *General intellectual functioning: WAIS-R IQ scores and aged scaled score*

 $NT = not tested$ .

Table *2 Recognition memory for faces and words: percentile scores*

	Case $11.4$			Case 11.5				Case $11.6$					
	Assessments												
	l st	2nd	3rd	l st	2nd	3rd	1st	2nd	3rd				
Faces Words		$\leq$ $<$ 1	NT <b>NT</b>	75	$\leq$ 1	NT NT	NT NT	$\leq$ 1 $\leq$	<। $\leq$ 1				

 $NT = not tested$ .

The educational and occupational histories of Cases II.5 and II.6 suggest that their intellectual levels premorbidly were at least within the upper limits of the average range. This is supported by an above average reading vocabulary [National Adult Reading Test (NART)] obtained on the second assessment of Case II.6. There was evidence of cognitive deterioration in both Cases II.5 and II.6 on the first assessment. Two years following each of these assessments both cases showed increasing global deterioration with the non-verbal scale affected to a greater extent. Furthermore, in both cases, the arithmetic subtest of the verbal scale showed greatest impairment. Further generalized cognitive decline was noted in the final assessments of Cases II.5 and II.6. In summary, verbal IQs were at somewhat higher levels than performance IQs in all cases. In the verbal domain, both Cases II.5 and II.6 showed the pattern of weak digit span and arithmetic as compared with vocabulary and similarities subtests *(see* Table I).

#### *Memory assessment*

The Recognition Memory Test (RMT) (Warrington, 1984) was administered to obtain a measure of verbal and visual memory function. The percentile scores of the three patients from each test occasion are shown in Table 2. At the first assessment, a severe global memory deficit was the only significant impairment in Case II.4. In Case II.5 there was evidence of a selective verbal memory deficit on the first assessment, although, on further testing, a more severe, global deficit was recorded. The first assessment of Case 11.6, included the revised Wechsler Memory Scale and performance was severely impaired for both visual and verbal material on recent and immediate recall tasks (WMS 66 and 52, respectively). By the time of the second assessment of all patients, recognition memory functions for both verbal and visual material were at chance levels. In summary, memory functions were severely and globally impaired in all three cases at a relatively early stage in the disease process.

#### *Literacy skills*

The assessment of literacy skills comprised individual tests of reading (Nelson, 1991), spelling (Baxter and Warrington, 1994) and arithmetic (Jackson and Warrington, 1986). Percentile scores for each patient at each assessment are given in Table 3. All patients demonstrated relatively intact reading skills, although these deteriorated across the second and third assessments of Case II.6. Spelling skills were entirely preserved in Case II.4, whereas these were shown to be deteriorating in the third assessments of Cases II.5 and II.6. Cases II.5 and Case II.6 showed impairment of arithmetic skills at the initial assessment, scoring below the fifth

	Case $11.4$			Case $11.5$				Case $11.6$				
	Assessments											
	l st	2nd	3rd	1st	2 <sub>nd</sub>	3rd	1st	2nd	3rd			
<b>NART</b>	75	75	75	50	50	NT	NT	75	50			
Spelling	75	90	90	25	25	10	NT	50	10			
Arithmetic	90	50	50	25	10		NT	$\leq$	$\leq$			
<b>GNT</b>	75	75	90	50	NT	NT	NT	50	50			

**Table 3** *Literacy and language: percentile scores*

 $NT = not tested$ .

**Table 4** *Perception and speed: percentile scores*

	Case $11.4$			Case $11.5$			Case $11.6$			
	Assessments									
	l st	2nd	3rd	l st	2nd	3rd	l st	2nd	3rd	
<b>Silhouettes</b>	25	75	50	NT	10	NT	NT			
Cubes	50	50	50	<b>NT</b>	$\leq$ 1	NT	<b>NT</b>	10		
Speed	50	NT		<b>NT</b>		NT	NT			

 $NT = not tested.$ 

percentile. Case II.4 showed a progressive decline of these skills from an initial superior to an average level. To summarize, arithmetic skills were more affected than reading and spelling in all three cases. As disease severity increased, spelling skills were also seen to deteriorate (Cases II.5 and II.6), whereas reading skills remained relatively spared.

# *Language skills*

The Graded Naming Test (GNT) was administered to obtain a measure of nominal skills (McKenna and Warrington, 1983). The percentile scores for each patient for each assessment are shown in Table 3. Case II.4 obtained relatively satisfactory and consistent scores across all assessments. The improvement noted may be accounted for by practice effects, indeed he professed to have revised some of the words from the GNT. Naming was relatively well preserved in both Case II.5 and Case II.6. The Oldfield Picture Naming test (Oldfield and Wingfield, 1965) was administered to both Cases II.5 and II.6 on their second and third assessments. Case II.5 scored 27 out of 30 and 23 out of 30, respectively, demonstrating a slight decline between assessments, and Case II.6 scored 21 out of 30 on both occasions. These findings clearly corroborate the average scores obtained by both patients on the stringent GNT. In summary, picture naming was remarkably well preserved in all three cases across all assessments.

# *Tests of perception and spatial skills*

Two subtests of the Visual Object and Space Perception Battery (VOSP) (Warrington and James, 1991), silhouettes and cube analysis, were administered to obtain a measure of perceptual and spatial skills, respectively. The percentile scores for each patient at each assessment are shown in Table 4. Overall perceptual skills were relatively intact in all three patients. However, the two most affected patients (Cases II.5 and II.6) were impaired on the spatial task.

# *Speed and attention tests*

Cognitive speed and attention were assessed using cancellation (Cases II.5 and II.6) and copying tasks (Case 11.4) (Willison *et al.,* 1980). The percentile scores for each patient at each assessment are shown in Table 4. The performance of Case II.4 deteriorated across assessments. At their most recent assessment each patient remained able to complete the task, although at an impaired level.

# *Tests of abstraction*

Two tests were employed: the simple, two category Weigl sorting task (Weigl, 1941) and the more demanding Wisconsin card sorting test (Nelson, 1976). Case **II.4,** at final testing, remained able to complete the Wisconsin card sorting task competently. Case II.5 performed competently on the Weigl on the first assessment, but failed it on subsequent administrations. Case II.6 failed this task from initial testing.

# *Speech production assessment*

Propositional speech production difficulties were a prominent feature of Cases II.5 and II.6 at a relatively early stage of their disease. Case II.4 showed hesitancy in his spontaneous

	Case $11.4$	Case $11.5$	Case $11.6$		
	Assessment				
	l st	l st	1st	2nd	3rd
	Sept. 10, 1991	Sept. 10, 1991	Sept. 10, 1991 Dec. 4, 1991		June 6, 1992
Reading Repetition	100 100	73 93	83 90	80 97	63 40

**Table 5** *Polysyllabic words: reading and repetition: percent correct scores*

**Table 6** *Repeating cliches and sentences: percent correct scores*

	Case $11.4$	Case $11.5$	Case $11.6$
<b>Clichés</b>	100	50	30
Sentences	100	80	60

speech, although this was not nearly as marked as in his siblings. These impairments of speech production were documented on tasks of word repetition and reading and sentence repetition and reading.

## *Word reading and repetition*

The test stimuli consisted of 30 three syllable, low frequency words (for details, *see* McCarthy and Warrington, 1984). The patients were asked to read and repeat these words in blocks of 15 using an ABBA design. The reading was self paced and in the repetition condition the words were spoken (unpaced) by the examiner. In addition to phonemic substitution, omission and repetition errors, false starts (bb-brown) were also scored as errors. There was a low but significant error rate for Cases II.5 and II.6 on both the reading and repetition task *{see* Table 5). However, for neither case was there a significant difference between the reading and the repetition conditions. Case II.4's performance on both these tasks was error free. When reassessed on this task 12 months after the first assessment Case II.6's performance had deteriorated *(see* Table 5).

## *Sentence repetition*

The test stimuli consisted of 10 novel sentences (e.g. I like peanuts) and 10 well-known clichés (e.g. 'red, white and blue'), matched for phrase length and complexity (for further details, *see* McCarthy and Warrington, 1984). The patients were requested to repeat novel sentences and clichés which were presented in blocks of five trials using an ABBA design. A strict scoring criterion was adopted; each was accepted as correct only if all words were pronounced correctly and in their correct order. The percent correct score for each sentence type for each patient is given in Table 6.

There was a significant error rate for Cases II.5 and II.6

on this repetition task. However, for neither patient was there a significant difference between the sentences and clichés on either task. Case II.4's performance on this task was error free.

## *Comment*

Cases II.5 and II.6 have similar speech production deficits. Although their impairments appear to be most pronounced in spontaneous speech, speech production errors have also been documented on formal tests of reading and repetition. Whereas the error rate on the single polysyllabic word repetition task was relatively low, their error rate increased on the harder task of repeating novel sentences and clichés. The patients' auditory-verbal short term memory and verbal comprehension were quite adequate for the task demands of repeating these short phrases. For neither patient was there any evidence of a task- or material-specific deficit. Overall, the errors were very comparable on the reading and the repeating tasks. In this regard neither patient conforms to the pattern of speech production impairment associated with a conduction aphasia or a transcortical motor aphasia. Thus, neither relative reliance on the automatic auditory/ phonological transcoding route nor relative reliance on a semantic route to speech production has been observed. It seems likely therefore that the locus of deficit in these patients occurs at, or after, a common language output system. The nature and variety of the speech errors; [e.g. *gigantic*— (ga d ant k); *lubricate*—(lub ge t); *exercise*—(ks s sa z)] with correctly articulated but incorrectly planned sound structure would suggest a deficit at a phonological, rather than phonetic level of representation.

## *PET*

Studies were performed on the Siemens ECAT 935B scanner at the MRC Cyclotron Unit, Hammersmith Hospital, London. The physical characteristics of this scanner have been described previously (Spinks *et at..* 1992). Permission to administer  $[{}^{18}F]$ fluorodeoxyglucose was obtained from the Administration of Radioactive Substances Advisory Committee (ARSAC) of the United Kingdom. Consent for this study was obtained from each individual, their carer, next of kin and general practitioner.

Continuous arterial sampling of radioactivity was performed following injection of  $5-10$  mCi of  $[{}^{18}F]$ fluorodeoxyglucose with calibration and glucose samples at 5, 10, 20 and 50 min. A dynamic series of 23 scans was acquired over a 60 min period following tracer injection. The resolution of images was  $8.0\times8.0\times4.3$  mm and the pixel size  $2.05\times2.05$ mm. Images spanning the last 30 min of the dynamic scan were added (add image) for further statistical analysis and for presentation purposes. Image analysis was performed on a SPARC II work station (SUN Microsystems, Europe Inc., Surrey, UK) using Imagetool software (CTI, Knoxville, Tenn., USA), Clickfit Software (MRC Cyclotron Unit, Hammersmith, London, UK) ANALYZE (Biodynamics Research Unit, Mayo clinic, Rochester, USA) [Robb and Hanson (1990)] and ProMATLAB (Math Works, Inc. Natick, Mass., USA).

A total of 16 cognitively normal volunteers were scanned to provide control data using an identical protocol. The mean age of the controls was 52 years (SD $\pm$ 11.1 years) with an age range of 31-71 years. All controls were asymptomatic, medication free and had no family history of dementia. The neurological and general medical examinations were normal and all scored more than 27 out of 30 on the MMSE.

Quantitative values for cerebral metabolic rate for glucose (cMRGlu) were calculated for 25 main regions of interest. A template of 400 sub-regions of interest was applied to the add image, using the atlas of Talairach and Tournoux (1988), to define the position of each region of interest. These were subsequently applied to the whole dynamic series of images in order to obtain tissue time activity curves for each region of interest. The blood time activity curve for each patient was fitted to the dynamic region of interest data and the metabolic rates for glucose were calculated using a four compartment model as described by Phelps *et al.* (1979). The lumped constant was taken as 0.52 (Reivich *et al.,* 1985). The second scan from each individual was co-registered and resliced to match the orientation of the first scan (Woods *et al.,* 1992). The same set of regions of interest was then applied to the dynamic series from the second scan.

Further data analysis was performed using statistical parametric mapping (SPM) (Friston *et al.,* 19916, *c).* The add images were standardized by transformation into a conventional stereotactic space (Friston *et al.,* 1989; Friston *et al.,* 1991a). The images were then smoothed using a Gaussian filter  $(20 \times 20 \times 10 \text{ mm})$  to minimize both the effects of individual variations in gyral anatomy and noise. These procedures generated a normalized set of 26 planes with an interplane distance of 4 mm corresponding directly to the atlas of Talairach and Tournoux (1988). Differences in global metabolic rate for glucose (gMRGlu) across all subjects and patients were normalized using an analysis of covariance (ANCOVA) technique (Friston *et al.,* 1990). The adjusted MRGlu for each voxel in each patient was compared with that found in the control group using the Z statistic. Significance scores were then displayed in three orthogonal planes as a statistical parametric map (Friston *et al.,* 19916).

The individual results are reported at an omnibus significance level of 0.001.

# *MRI*

The MRI scans were performed on an I.G.E. 1.5 tesla Signa Advantage MRI Scanner, at St Mary's Hospital, London at the same time as the PET studies. Routine axial proton density  $(2800/30/1 - TR/TE/NEX)$ , axial T2  $(2800/90/1 TR/TE/NEX$ ) and saggital T1 (500/10/2 - TR/TE/NEX) were performed with a 24 cm field of view and 256\*192 image matrix, 5 mm slice thickness and 2.5 mm interslice spacing. In addition, volumetric imaging was performed in the coronal plane using a spoiled echo gradient technique (SPG/R) yielding 124 1.5-mm thick contiguous slices through the head on a 256\*128 image matrix with aquisition parameters  $(35/5/1/35 - TR/TE/NEX/FLIP)$ . The MRI films were reported by a neuro-radiologist blind to the diagnosis and clinical details.

#### *Results of PET and MRI investigations*

Figure 3 shows the initial PET scan co-registered with the T<sub>2</sub>-weighted MRI images for Cases II.4, II.5 and II.6. Cases II.5 and II.6 have a similar symmetrical pattern of posterior parieto-temporal hypometabolism with additional frontal hypometabolism which is more apparent on the left. Case II.4 is more focal with an asymmetrical left temporal deficit and no frontal changes. The MRI scan shows generalized atrophy in all cases. Significant white matter signal changes are seen in Case II.6 but not in the initial scans of Cases II.4 and II.5. However, Case II.4 has white matter changes at the time of the second and third MRI scans *(see* Fig. 4). Both Cases II.4 and II.6 had a periventricular halo.

Table 7 shows the mean gMRGlu for each hemisphere for the three affected individuals and 16 normal controls (expressed as  $\mu$ mols/min/ml of brain tissue); a reduction in the gMRGlu, which became more pronounced by the time of the second scan, is noted in all the affected cases. In Case II.4 the right hemipshere gMRGlu is preserved when compared with the left side at the time of the first scan, although this is less apparent in the second scan. Table 7 also shows the sequential regional metabolic rate for glucose (rMRGlu) values for Cases II.4, II.5 and II.6. The rank position of each rMRGlu value is given so that one can determine the lowest and highest regional values for a given scan. Values lying two standard deviations from normal subjects are in bold. Case II.2 has a normal study and the regional values do not differ from those seen in the normal controls.

The lowest rMRGlu values in the first scan of Case II.4 (denoted by the lowest rank number) occur in the left supramarginal and inferior temporal gyri. This is also seen in Case II.5 where both right and left inferior temporal and supramarginal gyri are most affected. In Case II.6 the left superior temporal gyrus and inferior parietal lobe are slightly



 $Case II.4$ 



Case II .6

Fig. 3 PET and MRI images for each individual. The PET data set has been co-registered onto the MRI data set. A biparietal bitemporal deficit with additional frontal hypomentabolism is seen in Cases II.5 and II.6 who are the more severely affected. A focal left temporal deficit is seen in Case II.4. The scan is displayed so that the right hand side of the figure is the right side of the brain.

 $\sim$   $\frac{1}{2}$ 

lower than the left supramarginal and inferior temporal gyri. The right supramarginal gyrus value is relatively preserved in Cases II.6 and II.4 as denoted by the high rank number and rMRGlu values well within the normal range.

Case II.5's second scan shows the same pattern as before with bilateral inferior temporal and supramarginal gyri being most severely affected, although the deficit is more widespread and more regions have significant hypometabolism. In Case II.6 the right supramarginal gyrus has decreased with a marked change in its rank position (from 15 to five) and both right and left supramarginal gyrus are now significantly below normal. The inferior parietal and superior temporal values are now lowest bilaterally. In Case II.4 the right supramarginal and middle temporal value have decreased with a change in their rank order, but the left inferior parietal lobule and left supramarginal gyrus remain the most severely affected and both are now significantly reduced.

More left hemisphere regions show significant hypometabolism than equivalent right hemisphere regions. Indeed both Cases II.4 and II.6 have only one significant region at the time of the first scan. Both Cases II.6 and II.5 have a similar pattern of frontal hypometabolism involving the left superior, middle and inferior frontal gyri more than the right, which is best seen in the clustering of significant regions of deficit in the left frontal region in second scan. Both of these individuals have the speech production deficit.

Figure 5 shows the SPM images for each individual which reflect relative changes in the distribution of metabolism

<u>Livia Liberation</u>



Fig. 4 Case II.4. T<sub>2</sub>-weighted MRI images. Periventricular white matter changes are visible in these two T<sub>2</sub>-weighted scans. The upper scan was taken at the time of Assessment 3, the lower scan at the time of the subsequent examination. (The scan is displayed so that the right hand side of the figure is the right side of the brain.)

compared with 16 cognitively normal controls *(P <* 0.001). The SPM analysis produces similar patterns of relative hypometabolism for each individual. We have tried to eliminate the possibility that the results are due to errors in image processing, due, for example, to comparison of atrophied brains with normal non-atrophied brains. Significant areas of hypometabolism are not found in relation to sulci and thus we feel that cerebral atrophy is not the predominant reason for the metabolic profiles, although it may contribute. An identical analysis of randomly selected normal individuals against the normal control group does not produce the patterns of hypometabolism seen in this family. Previous studies have shown that cerebral atrophy may lead to partial volume effects which may underestimate cerebral glucose metabolism. No simple method exists for correction of this error and we were therefore unable to adjust the SPM or regions of interest data for atrophy.

The diagrams illustrate the progression of the disease and show increases in the extent of the hypometabolism with time. The distribution of relative decreases in metabolism from each of the subjects is strikingly similar with diffuse significant changes in temporo-parietal cortex bilaterally. This pattern is confirmed by a quantitative regions of interest analysis. A number of distinct regions are significantly hypometabolic in all three subjects. Cases II.5 and II.6 who share the speech production deficit have a similar pattern of left frontal hypometabolism involving Broca's area which

is not seen in Case II.4 who does not have the speech production deficit.

#### **Discussion**

This chromosome 14 linked pedigree is characterized not only by similarities in the individual clinical course, but by the consistent neuropsychological profile with a similar pattern of cognitive dysfunction at equivalent stages of disease severity. Likewise, the metabolic data show similarities in the regional distribution of hypometabolism which is in good accord with the cognitive deficits. The pathological features are entirely typical of Alzheimer's disease, namely senile plaques, neurofibrillary tangles and amyloid angiopathy.

# *Clinical features*

Memory impairment was the presenting complaint in all three cases; however, personality change was also noted early in Case II.5. Word retrieval skills were well preserved in this pedigree, although speech production difficulties became prominent at an early stage in two cases. All individuals maintained insight into their cognitive symptoms. The most severely affected case had the longest duration and the least affected the shortest, suggesting a similar rate of progression in each individual.

The neurological examination revealed myoclonic jerks

	Case 11.4: scan 1		Case 11.4: scan 2			Case 11.5: scan 1		Case 11.5: scan 2		Case 11.6: scan 1		Case 11.6: scan 2		normals	
	<b>MRGIu</b>	Rank	<b>MRGIu</b>	Rank	<b>MRGIu</b>	Rank	MRGlu	Rank	<b>MRGlu</b>	Rank	<b>MRGlu</b>	□ Rank	$(n = 16)$ <b>MRGlu</b>	$-2$ SD	$+2SD$
(A) Left hemisphere												loaded			
Regions of interest															
Cingulate gyrus	0.4535	16	0.3575	10 <sup>2</sup>	0.4532	15	0.3878	17	0.3793	5	0.3532	lien.	0.5696	0.2722	0.8671
Medial frontal gyrus	0.5191	19	0.3870	15	0.4107	12	0.3884	18	0.4052	$\overline{7}$	0.3743	₽	0.5319	0.2804	0.7834
Inferior frontal gyrus	0.3545	6	0.4057	16	0.4025	10	0.2935	10	0.4325	12	0.3344	$\frac{1}{2}$	0.5672	0.3266	0.8077
Middle frontal gyrus	0.4642	18	0.4080	17	0.3015	3	0.2732	$\overline{7}$	0.4318	$\mathbf{1}$	0.2871		0.5616	0.3129	0.8103
Superior frontal gyrus	0.4592	17	0.4105	18	0.3398	5	0.2814	-8	0.4171	$10^{\circ}$	0.2801	yora∏ G	0.5135	0.3258	0.7012
Orbital gyrus	0.3664	$\overline{7}$	0.3673	12	0.4085	$\mathbf{11}$	0.3617	12	0.4583	17	0.3562	37	0.5549	0.3154	0.7945
Inferior occipital gyrus	0.3447	3	0.3782	13	0.4283	13	0.2825	9	0.4116	9	0.3031		0.5040	0.2195	0.7885
Medial occipital gyrus	0.4369	15	0.3451	$\overline{7}$	0.5288	21	0.3654	4	0.4420	15	0.3271	Rord	0.5372	0.3212	0.7533
Post central gyrus	0.3772	8	0.3369	5	0.4412	14	0.3931	19	0.4111	8	0.3266	$\overline{2}$	0.5374	0.3114	0.7634
Precentral gyrus	0.3796	9	0.3788	14	0.4565	16	0.4015	20	0.4403	$\overline{14}$	0.4074		0.5551	0.3243	0.7859
Supra marginal gyrus	0.3282	$\mathbf{1}$	0.2950	$\overline{2}$	0.2554	$\overline{2}$	0.2149	$\mathbf{I}$	0.3453	$\overline{4}$	0.2537	rnals.	0.5739	0.2874	0.8605
Inferior temporal gyrus	0.3333	$\overline{2}$	0.3087	3	0.2156	$\mathbf{I}$	0.2332	$\overline{2}$	0.3243	3	0.2642		0.4990	0.3480	0.6500
Middle temporal gyrus	0.3472	$\overline{4}$	0.3405	6	0.3541	$\overline{7}$	0.2332	3	0.4020	6	0.2991		0.5371	0.3541	0.7201
Superior temporal gyrus	0.4199	$12 \,$	0.3496	8	0.3082	4	0.2557	5	0.2779	1	0.2448	pous voisuest	0.5029	0.2972	0.7086
Inferior parietal lobule	0.3938	$\mathbf{1}$	0.2781	$\mathbf{I}$	0.3574	8	0.2549	$\overline{4}$	0.3143	$\overline{2}$	0.2346		0.5550	0.3236	0.7864
Superior parietal lobule	0.3846	10	0.3541	9	0.3465	6	0.2648	6	0.4352	13	0.2628		0.5962	0.2922	0.9002
Caudate nucleus	0.5685	20	0.5750	21	0.4979	18	0.3644	$\overline{13}$	0.5562	21	0.3255	≨⊖	0.5293	0.2609	0.7977
Putamen	0.5785	21	0.4547	19	0.5083	19	0.4371	21	0.4662	18	0.4017		0.5861	0.3012	0.8711
Precuneous	0.4204	13	0.3584	$\mathbf{11}$	0.3809	9	0.2956	$\mathbf{11}$	0.4466	16	0.3411	曾	0.6016	0.3176	0.8856
<b>Thalamus</b>	0.4266	14	0.4794	20	0.4757	17	0.3862	15	0.4753	19	0.3425	$\overline{5}$	0.5896	0.3254	0.8537
Cerebellum	0.3525	5	0.3328	$\overline{4}$	0.5195	20	0.3876	16	0.4958	20	0.3626		0.4892	0.3284	0.6500
Global MRGlu	0.3594		0.3579		0.3983		0.3241		0.4196		0.3238	$rac{1}{2}016$	0.5202	0.3320	0.7084
<b>(B)</b> Right hemisphere Regions of interest															
Cingulate gyrus	0.4738	16	0.4069	15	0.3870	8	0.3386	13	0.3571	4	0.3683	18	0.5417	0.3167	0.7667
Medial frontal gyrus	0.3599	$\mathbf{1}$	0.3719	9	0.3591	6	0.4091	19	0.2329	$\mathbf{1}$	0.3478	15	0.5615	0.2800	0.8430
Inferior frontal gyrus	0.4165	6	0.3832	$\mathbf{H}$	0.4021	10	0.3333	12	0.4729	16	0.3214	10	0.5330	0.3450	0.7210
Middle frontal gyrus	0.4553	13	0.3959	12	0.3525	5	0.2821	7	0.4517	13	0.3295	11	0.5407	0.3509	0.7304
Superior frontal gyrus	0.4665	14	0.4028	14	0.4050	$\mathbf{1}$	0.2986	9	0.4280	9	0.2859	$7\overline{ }$	0.5050	0.2959	0.7141
Orbital gyrus	0.5213	19	0.4239	17	0.4543	17	0.3580	14	0.4996	19	0.3509	16	0.4863	0.2671	0.7054
Inferior occipital gyrus	0.4187	7	0.4838	19	0.4467	15	0.3258	$\mathbf{11}$	0.4386	$\mathbf{H}$	0.2826	6	0.5212	0.3370	0.7055
Medial occipital gyrus	0.4933	17	0.3298	3	0.5386	21	0.3794	15	0.4583	14	0.3302	12	0.5248	0.3285	0.7210
Post central gyrus	0.4395	9	0.3663	$\overline{7}$	0.4355	$\overline{14}$	0.4025	18	0.4245	8	0.3683	17	0.5142	0.3187	0.7096
Precentral gyrus	0.4444	12	0.4084	16	0.4502	16	0.4014	17	0.4790	18	0.3981	20	0.5281	0.3230	0.7333
Supra marginal gyrus	0.4436	Ħ	0.3238	$\overline{2}$	0.3214	$\overline{2}$	0.2337	$\mathbf{I}$	0.4594	15	0.2696	5	0.5637	0.3023	0.8250
Inferior temporal gyrus	0.3946	3	0.3770	10	0.2107	$\mathbf{I}$	0.2786	4	0.2670	$\overline{2}$	0.2877	8	0.4583	0.3225	0.5941
Middle temporal gyrus	0.4081	5	0.3093	$\mathbf{I}$	0.3411	3	0.2760	3	0.3744	5	0.3085	9	0.5067	0.3097	0.7037
Superior temporal gyrus	0.4015	4	0.3439	4	0.3443	4	0.2878	8	0.3518	3	0.2371	J.	0.4904	0.3075	0.6734
Inferior parietal lobule	0.4341	8	0.3965	13	0.3695	$\overline{7}$	0.2696	2	0.3964	6	0.2419	$\overline{c}$	0.5428	0.3163	0.7692
Superior parietal lobule	0.4435	10	0.3520	5	0.4223	12	0.2817	6	0.5400	21	0.2536	3	0.5941	0.3333	0.8549
Caudate nucleus	0.5534	20	0.5330	21	0.5078	19	0.4167	20	0.5199	20	0.2547	$\overline{4}$	0.5646	0.3189	0.8104
Putamen	0.6239	21	0.3682	8	0.5193	20	0.4333	21	0.4372	10	0.3898	19	0.5497	0.3528	0.7465
Precuneous	0.4718	15	0.4493	18	0.4015	9	0.3066	10	0.4212	-7	0.4206	21	0.5748	0.3995	0.7501
<b>Thalamus</b>	0.5058	-18	0.4978	20	0.4705	18	0.3934	16	0.4419	12	0.3425	13	0.5702	0.3521	0.7883
Cerebellum	0.3932	$\overline{2}$	0.3556	6	0.4295	13	0.2802	5	0.4771	17	0.3465	14	0.5048	0.3362	0.6734
Global MRGlu	0.4035		0.3472		0.4101		0.3321		0.4232		0.3222		0.5151	0.3465	0.6838
Values which fall below 2 SD of normal are indicated in bold.															

Table 7 Left (A) and right (B) hemisphere MRGlu values ( $\mu$ mol/min/ml) for each of the subjects and normal controls with the relative rank position of each value

Mean



**Fig.** 5 SPM Z maps. This figure show the distribution of the Z statistic at a significance threshold *P <* 0.001. The black areas reflect those areas showing significant hypometabolism when compared with 16 cognitive normal control cases. The Z maps for scans 1 and 2 are shown for each case. Each scan is shown in three projections: sagittal *(top left)*, coronal *(top right)* and transverse *(bottom)*. The letter R indicates the right side of the brain. The scan is displayed so that the right hand side of the figure indicates the right side of the brain.

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which were present at a relatively mild stage of dementia severity, whereas other features such as apraxia were only found when the individuals were more severely affected. Studies of sporadic Alzheimer's disease suggest that myoclonus and seizures represent features which reflect disease severity (Hauser *et al.,* 1986; Chen *et al.,* 1991). By contrast, myoclonic jerks are prominent in some pedigrees with familial Alzheimer's disease (Sadovnick *et al.,* 1988) and indeed have been reported to predate cognitive impairment (Jacob, 1970). The presence of myoclonus in all the affected members of this family provides further evidence that this is a frequent finding in young onset familial Alzheimer's disease families. However, only one patient from this family was documented to have seizures unlike the British family with an APP 717  $_{val—gly}$  mutation, where seizures were a frequent observation (Kennedy *et al.,* 1993).

It has been proposed that the underlying specific genetic defect in familial Alzheimer's disease may partly determine the age at onset (van Duijn *et al., \99\b).* The detailed assessment of three individuals with an identical genetic aetiology allows the relationship of possible epigenetic factors to be examined. There are a variety of reported risk factors for Alzheimer's disease, of which head injury has been consistently observed (Graves *et al.,* 1990; Mortimer *et al.,* 1991). It is interesting, therefore, that both our younger cases had significant head injuries prior to the start of their illness, whereas Case II.4 did not. Similarly, the two deceased individuals with ages at onset of 43 and 45 years, respectively, also had head injuries prior to the onset of cognitive decline. Head injury has been shown to lead to  $\beta$ -amyloid deposition, which may be a common response to neuronal injury (Roberts *et al.,* 1991). In an individual already genetically predisposed to Alzheimer's disease this may accelerate such a process and lead to an earlier age at onset.

The presence of oligoclonal bands in the cerebrospinal fluid (CSF) of Case II.4 was unexpected, although increased CSF immunoglobins have been described in Alzheimer's disease (Williams *et al.,* 1980; Chu *et al.,* 1983; McLean *et al.,* 1990). These studies have shown variable results. Williams *et al.* (1980) found that five out of eight individuals with pre-senile dementia had positive oligoclonal bands. Others have found either no association whatsoever (Chapel *et al.,* 1984) or only that a very small proportion of cases have increased CSF Ig G synthesis (Chu *et al.,* 1983; McLean *et al.,* 1990). Cases of dementia with clinical features similar to multiple sclerosis but with pathological evidence of demyelination and an associated amyloid angiopathy but without Alzheimer histopathology have also been reported (Heffner *et al.,* 1976). The symptoms and clinical course of Case II.4 are consistent with Alzheimer's disease, as is the pattern of cognitive impairment. There were no physical signs to suggest multiple sclerosis and the visual and sensory evoked potentials were normal. No oligoclonal bands were observed in Case II.5 who is the only other family member to have had a CSF examination. The white matter changes observed in the MRI scan of both Cases II.4 and II.6 have

been documented frequently in sporadic Alzheimer's disease (Kozachuk *et al.,* 1990) and aged matched normals (Leys *et al.,* 1990), as well as cases with amyloid angiopathy (Haan *et al.,* 1990), and therefore are not pathognomonic of any one condition. Additional neuroimaging in Case II.4 suggests that the lesions are unlikely to be inflammatory.

# *Neuropsychology*

The neuropsychological profile was one of generalized intellectual decline with impairment of recognition memory functions, arithmetic skills and speech production in the context of relatively preserved reading, spelling, naming and verbal comprehension skills. This pattern of deficits became more pronounced with disease progression.

A deficit in recent memory function is a classic, early and diagnostic feature of both sporadic Alzheimer's disease and familial Alzheimer's disease (Rosen and Mohs, 1982; Crapper McLachlan *et al.,* 1984; McKhann *et al.,* 1984; Haxby *et al.,* 1986; Grady *et al.,* 1988; Karlinsky *et al.,* 1991, 1992) as is the case in Family 148. In Case II.4 impairment of recognition memory functions occur in the context of otherwise preserved cognitive functioning and there was a clear selective verbal memory deficit observed at the first assessment of Case II.5. This observation, considering the known lateralizing power of the RMT (Warrington, 1984), implies a greater left hemisphere vulnerability to disease onset in this family, a conclusion that receives support from the PET data.

Acalculia has previously been reported as a feature of the neurological examinations in some affected individuals from large Alzheimer pedigrees (Nee *et al.,* 1983) including both chromosome 14 linked and APP 717 pedigrees (Karlinsky *et al.,* 1991; Kennedy *et al.,* 1993). The longitudinal assessments of our family in this study show arithmetic skills to be universally affected with relative preservation of reading and spelling skills; this discrepancy can be seen best across the assessments of Case II.4, where arithmetic skills are observed to decline whilst other literacy skills are maintained at optimum levels. This finding further supports the notion that acalculia is a feature of young onset or familial Alzheimer's disease. It is not clear why such a focal function should be selectively impaired in this way by the disease.

A previously undocumented feature of the neuropsychological profile in this family is the particular pattern of language deficit: impaired spontaneous speech output together with intact naming skills and relative sparing of comprehension was observed in both Cases II.5 and II.6. This differs from previous reports of the prevalence of Wernicke's aphasia in Alzheimer's disease (Cumming *et al.,* 1985; Benke *et al.,* 1990; Lang *et al.,* 1991). The stuttering, hesitancies and frequent phonemic paraphasias made by these two patients suggest a common deficit in the language output mechanisms. The nature and specificity of this deficit is perhaps the strongest phenotypic evidence for genetic homogeneity in this family. It remains to be seen whether this pattern of speech production deficits will appear in Case

## *Neuroimaging*

Cerebral metabolism was globally reduced with an emphasis in the temporal and parietal cortex, a finding that is similar to observations in sporadic Alzheimer's disease (Frackowiak *et al.,* 1981; McGeer *et ai,* 1986; Haxby *el al.,* 1987). Cases II.5 and II.6 who have the speech production deficit, both have additional left-sided frontal hypometabolism seen best in Figs 3 and 4. This is clearest from the SPM analysis where it can be seen to involve Broca's area. The least affected case (II.4) shows a more focal left temporal deficit reflecting a more circumscribed clinical and neuropsychological profile. In all three individuals the left hemisphere was disproportionately affected at an early stage of the disease, an asymmetry that was most apparent in Case II.4.

The neuropsychological tests also implicate initial left hemisphere vulnerability in Case II.5. The PET data show a more severe left-side deficit in the two lesser affected patients which is best observed in the ranked rMRGlu data (Table 7) for Cases II.4 and II.6. The follow-up scans show that the asymmetry is less apparent later in the disease. The regions of maximal hypometabolism are very similar in Cases II.4 and II.5, but less so in Case II.6. However, frontal hypometabolism is seen in both individuals with a speech production deficit. Other PET (Duara *et al.,* 1986; Haxby *et al.,* 1986; Loewenstein *et al.,* 1989), neuropsychological (Seltzer and Sherwin, 1983; Martin *et al.,* 1985; Capitani *et al.,* 1990) and neurochemical (Rossor *et al.,* 1982) studies have also shown left hemisphere asymmetries. What is of considerable interest is the sparing of the left frontal cortex around Broca's area in the least affected patient without the speech production deficit, whereas the two individuals with the speech production deficit have involvement of this area.

Several studies have examined familial cases with a younger age at onset, but not individuals from the same pedigree and thus with the same aetiology. Cutler *et al.* (1985) assessed an individual from a familial Alzheimer's disease pedigree with an isolated memory deficit, with normal naming and visuospatial skills. Sequential neuropsychological examinations on three occasions showed no alteration in these deficits. However, despite a normal first scan his second scan showed bilateral superior parietal hypometabolism and right lenticular hypermetabolism. By the time of the third scan right caudate and lenticular metabolism was increased and the whole parietal lobe was hypometabolic. Polinsky *et al.* (1987) studied a 55-year-old female and a 42-year-old female, both with a moderate degree of dementia from two large previously described pedigrees. Both individuals had a temporo-parietal deficit with maximal hypometabolism in the temporal lobe and supramarginal gyms bilaterally. One 'at risk' subject had left supramarginal gyms hypometabolism but no clinical details are given other than that he was

asymptomatic. Our family shows similarities to that of Polinsky, with supramarginal gyrus hypometabolism as an early and prominent feature.

# *Comparison with other chromosome 14 linked pedigrees*

This family has a mean age at onset of 43 years and in common with the majority of other chromosome 14 linked families is relatively younger than that reported in the APP families (Chartier Harlin *et al.,* 1991; Goate *et al.,* 1991; Murrell *et al.,* 1991; Naruse *et al.,* 1991; Yoshioka *et al.,* 1991; Fidani *et al.,* 1992; Karlinsky *et al.,* 1992; Mullan *et al.,* 1992a; Kennedy *et al.,* 1993; Sorbi *et al.,* 1993). In the study by Schellenberg *et al.* (1992), families L and SNW show the strongest linkage to chromosome 14. Family L is of German extraction and has a mean age at onset of 42 years. This family was included in a study of 24 early-onset kindreds that provide evidence for phenotypic heterogeneity (Bird *et al.,* 1989). The individuals with a younger age at onset (which includes members of Family L) were found to have a higher incidence of myoclonus, language deficit, seizures and extrapyramidal signs which were suggested as being a more frequent manifestation of familial Alzheimer's disease. Family SNW of Russian-Jewish extraction had been described by Goudsmit *et al.* (1981) and a total of 10 cases have come to post-mortem. The mean age at onset in this family was 52 years. No detailed clinical findings were described but it is emphasized that no myoclonus, seizures or extrapyramidal signs were observed, although pyramidal signs were a frequent finding. Recently, the detailed neuropsychology from this family has been published. Mildly impaired verbal performance and concentration, as well as slow psychomotor speed and recall of verbal material characterized the cognitive impairment which was not significantly different from the observations in a group of sporadic cases (Swearer *et al.,* 1992). These findings are qualitatively different from our observations in this family. Few clinical details are available for the families reported in the genetic linkage study of St George-Hyslop *et al.* (1992). Van Broeckhoven (1992) showed linkage in the two Belgian families A and B, described by van Boegart *et al.* (1940) and by Martin *et al.* (1991). The mean age at onset in Family A was 35.1 years characterized by rapidly progressive memory loss, disturbance of affect and language impairment. Neurological features included gait impairment, extrapyramidal features, pseudobulbar signs, myoclonus and epilepsy, but no pyramidal or cerebellar signs. Family B had an age at onset of 34.7 years with cerebellar signs being observed early in the disease, whereas myoclonus, epilepsy and pyramidal signs were later features.

A wide range of clinical features have been described in families which show chromosome 14 linkage to which an early speech production abnormality and evidence of left hemisphere vulnerability can now be added. This clinical

variability, together with a consistent pattern within a single pedigree, would be compatible with allellic heterogeneity at the chromosome 14 locus. If this is correct, then variability in the molecular genetic abnormality would be predicted to determine the phenotype and other pedigrees with the same clinical phenotype should share the same mutation.

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# **Appendix 1**

*Case histories*

*Deceased affected*

*Case I.I.* Age at onset: 40 years. Age at death: 44 years. Duration: 4 years.

No clinical details are available other than that she died at the age of 44 years following a 4-year history of cognitive impairment.

*Case 1.2.* Age at onset: 43 years. Age at death: 49 years. Duration: 6 years.

This printer was first noticed to have cognitive disturbance at the age of 43 years when his wife described him as forgetful and his son recalled him forgetting to put his clothes on and getting lost on the way home from work. During his working life he sustained a head injury, although it is not recorded whether he lost consciousness. He died at the age of 49 years from tuberculosis and a lung abscess The death certificate records a cerebro-vascular accident as the cause of death in addition to the tuberculosis.

*Case II. I.* Age at onset: 43 years. Age at death: 53 years. Duration: 10 years.

This right-handed female left school at the age of 18 years. She went to technical college and obtained a qualification in chemistry before working as a laboratory technician. At the age of 19 years she was involved in a cycling accident and sustained a head injury with a laceration to the left eye. She was concussed for  $\sim 20$  min. There were no neurological sequelae and she made an immediate recovery. Her past medical history was otherwise unremarkable.

At the age of 43 years she enrolled in a teacher training course, but left suddenly and without explanation. Two months after this her husband recalls her being involved in a minor road traffic accident. Subsequently she was unable to recall attending a musical concert and from this time he observed her to be uncharacteristically belligerent and aggressive towards her children. Her forgetfulness progressed and she became lost whilst on holiday that year.

At the age of 45 years her general practitioner referred her to a local physician who noticed 'shaking' in her hands

and elicited a glabellar tap reflex. A trial of levodopa was unsuccessful and she was referred for neurological assessment. Her memory and intellect were found to be impaired on bedside testing, but speech was normal. There were no focal neurological signs and she was not thought to have any features of Parkinson's disease. Routine blood investigations including vitamin  $B_{12}$ , thyroid function, treponemal serology and CSF examination were all normal. A radio-nucleotide brain scan was normal and an air encephalogram showed cerebral atrophy. An EEG showed a dominant alpha rhythm with slow waves bi-temporally. A diagnosis of pre-senile dementia was made.

At home she was able to cope with the housework, although she was irregular in preparing meals. Her husband felt that she had some degree of insight in that she would exclaim, 'O God it is terrible' and if pressed to remember something she would become emotional. At the age of 47 years she was admitted for long-term care. Twitching was noted in her arms in the absence of disturbance of consciousness and she subsequently had several generalized seizures which were treated with sodium valproate. An EEG was repeated but no epileptiform changes were seen in association with the jerking. In view of the frequent seizures and frequent muscular jerkings a diagnosis of Huntington's chorea was considered. She died of bronchopneumonia at the age of 53 years.

The brain, which weighed 922 g after fixation, was severely atrophic. Naked eye examination showed marked generalized narrowing of the cerebral gyri and widening of the sulci (Fig. Al, A-C) but no specific localized abnormality. The cerebral vessels were normal.

Coronal sections showed widely dilated ventricles with narrowing of the cortical ribbon and reduction of the subcortical white matter. The caudate, putamen and globus pallidus were smaller than normal in proportion to the degree of general atrophy. The histological appearance showed typical features of severe Alzheimer's disease with large numbers of senile plaques and neurofibrillary tangles throughout the cerebral cortex (Fig. A1, D and E). The cortical nerve cells were reduced in number and there was a



Fig. A1 Neuropathology. (A) Lateral view of brain showing marked narrowing of the gyri. (B and C) Two coronal slices of the left cerebral hemisphere cut at the amygdaloid level and the anterior hippocampal level, respectively, show severe dilatation of the lateral ventricle with marked reduction in the width, both of the cortical ribbon and the subcortical white matter. (D and E) The histological appearance showed typical features of severe Alzheimer's disease with large numbers of senile plaques and neurofibrillary tangles throughout the cerebral cortex. Stain: von Braunmuhl;  $\times$ 200 (D) and  $\times$ 260 (E).

marked generalized gliosis of both cortex and white matter. There was no macroscopic or histological evidence of Huntington's disease.

*Case III.3.* Age at onset: 43 years. Age at death: 49 years. Duration: 7 years.

This right-handed man left school at the age of 15 years without qualifications. His handwriting had always been poor; however, his reading and mathematics were satisfactory. He worked as a lorry driver and as a boiler maker. His medical history was unremarkable. However, he sustained a number of minor head injuries and was briefly knocked unconscious when, at the age of 25 years, he fell off a lorry. He and his wife emigrated to South Africa when he was 35 years old. They returned to the UK 6 years later and at the age of 42 years his wife noticed that he had difficulty hanging some wallpaper. Following this he misjudged the distance whilst reversing his lorry, causing significant damage. His memory was mildly impaired at this stage but his speech was completely normal.

They returned to South Africa when he was 44 years old and he was reinstated in his old job as a boilermaker. It was evident that he was having considerable difficulties; for example, he took more than 2 h to rewire a plug. He told his wife that something was seriously wrong and he asked his doctor for referral to a neurosurgeon, who made a diagnosis of pre-senile dementia. He continued with his job until he was involved in a serious road traffic accident when he failed to recognize a red light.

He became difficult to manage at home and was admitted to a nursing home. At this stage his speech was affected but he was not noted to stammer or stutter. He died of bronchopneumonia at the age of 49 years. A post-mortem was not performed. There was no history of myoclonic jerks or seizures.

### *Living affected*

*Case 11.4.* Age at onset: 48 years. Current duration: 7 years. This 55-year-old right-handed man left grammar school at the age of 16 years with six 'Ordinary' level passes. He served an apprenticeship in the textile industry and then worked as a council surveyor until the age of 50 years. His past medical history was unremarkable. He was occasionally breathless on exertion but this was attributed to his lifelong habit of smoking 20 cigarettes per day.

At the age of 48 years, his wife first noted that he forgot recent events and began to repeat himself. He had progressive difficulties performing his job and was dismissed without clear explanation. In the year following this, he was briefly employed in two further positions, although he was dismissed from both after only 6 months.

In the year preceding the first assessment his memory had gradually deteriorated and he now kept written notes to remind him of his daily activities. He was unable to recall meeting people and was observed to put objects in strange

places (e.g. soap in the cutlery drawer). His vocabulary was normal; however, his wife found his speech uncharacteristically hesitant. He continued to drive a motor car safely and had no obvious difficulty finding his way about the neighbourhood. He participated in some hobbies including skiing, gardening and solving crossword puzzles. He had considerable insight into his memory difficulty.

Neurological examination was normal throughout including visual acuity, colour vision, fundoscopy, saccadic and pursuit eye movements and co-ordination. The reflexes were symmetrical, plantar responses flexor and the abdominal reflexes preserved. Sensory examination was entirely normal. Tests of praxis were normal and no primitive reflexes were elicited. The MMSE scores were shown to decline (Fig. 2) at each assessment and myoclonic jerks were noted at the time of the second examination.

At the time of Examination 1, an EEG revealed focal left temporal disturbances with well-preserved background. The **MRI** scan showed mild diffuse cortical atrophy, but no white matter lesions. Examination of CSF revealed normal microscopy and CSF protein of 0.54 g/1 with oligoclonal bands. Oligoclonal bands were present both in the serum and the CSF but with a different electrophoretic pattern. A further neuropsychological assessment was made at the time of Assessment 2.

The clinical examination was unchanged at the time of Examination 3. On this occasion myoclonic jerks were noted in addition to body part substitution errors during tests of praxis. A repeat MRI scan again showed mild cortical atrophy and in addition multiple periventricular white matter lesions were seen (see Fig. 4, upper scan). The CSF examination again revealed oligoclonal bands. Visual evoked potentials were normal.

An additional clinical assessment was made in May 1993 when further evidence of deterioration was observed. He now scored 17 out of 23 on the MMSE but still had a CDR of 1. The neurological examination was unchanged. A further **MRI** scan again showed white matter lesions which did not show enhancement with gadolinium *(see* Fig. 4, lower scan). A magnetic transfer contrast scan was performed and was considered not consistent with multiple sclerosis. Hydrogen spectroscopy showed a fall in the  $N$ -acetylaspartate (NAA) peak which was thought to reflect non-specific neuronal damage (Gass *et al.,* 1993). Further visual and sensory evoked potentials were again normal.

*Case II.5.* Age at onset: 43 years. Current duration: 8 years.

This right-handed twin left school at the age of 16 years with four 'Ordinary' level passes to pursue a career in the army. He attained the rank of warrant officer and at the age of 40 years he passed an additional qualification in business management. His past medical history was unremarkable, although at the age of 42 years he hit his head and grazed the right side of his face; there was no loss of consciousness but he was reported to be mildly concussed.

At the age of 43 years he returned from a tour of duty

and his wife noted that he was uncharacteristically aggressive and dated the progressive cognitive disturbance from that time. A year later he was withdrawn from active service to adopt an administrative position. At the age of 46 years he was fully investigated, although no clear diagnosis was established and he was discharged from his post as a careers officer the following year. At the age of 47 years he was assessed for the first time at the National Hospital. He forgot things that he had been told and had difficulty completing paperwork in his office job. His speech had become hesitant but he managed to drive his car and continue his hobbies.

When seen for the second assessment (age 50 years) his speech had deteriorated and he was now stuttering. His wife also noted that he would point at objects in preference to describing them. He had recently ceased to drive a car. He would spend all day trying to complete a crossword puzzle and now took no interest in his stamp collection. He managed to run in his locality without getting lost; however, he had become lost whilst on holiday abroad. Throughout he retained reasonable insight into his difficulties and at times would be tearful.

By the time of the last assessment he was often unable to recognize his family and would become agitated if left alone. He was still able to dress himself, although he had difficulty with buttons and shoelaces. His speech had deteriorated further and he was unable to sign his name or read.

Successive MMSE values and CDR scores document the progressive decline (Fig. 2). Neurological examination was normal at the first assessment. Myoclonic jerks were prominent in both fingers and toes especially on the left side at the time of the second evaluation. There was reduced speech output with stuttering and stumbling over his words. He had difficulty copying gestures and made occasional body part substitutions in miming the use of objects. A pout reflex was elicited but no other primitive reflexes were found. Clinical examination at the third assessment was unchanged, although there was increased difficulty with miming and copying gestures.

An EEG revealed a left temporal disturbance of a non specific nature. The MRI scan showed a mild degree of atrophy and the hippocampus was irregular in outline bilaterally. No white matter lesions were observed. Examination of CSF was entirely normal.

*Case 11.6.* Age at onset: 45 years. Current duration: 6 years.

This single left-handed woman left school at the age of 16 years with six 'Ordinary' level passes and worked archiving newspaper cuttings for a local newspaper. At the age of 40 years she fell from her horse whilst riding and was knocked unconscious for 2 h, although there was no skull fracture. Her medical history was otherwise unremarkable.

Her elder brother recalls her having difficulties solving problems at the age of 45 years, for example, when they both participated in an inflatable boat race she was unable to navigate obstructions in the water. At this time she was also found to mislay simple items such as keys and combs.

She remained fully independent at home caring for her elderly mother. She finally left her job at the age of 49 years as she was unable to cope with her duties. She was assessed at her local hospital at this time and underwent initial neuropsychological testing.

In the year prior to the second assessment she continued to live at home by herself, although she used a list to remind herself of her daily activities and was able to drive a motor car safely. She managed her hobbies of riding and singing in a local choir. Her speech was hesitant and she had developed a stammer during the previous 12 months. She had great insight into her predicament and became tearful with frustration at being unable to remember.

Prior to the third assessment, she had deteriorated considerably and had great difficulty with her speech which was hesitant and limited to simple phrases such as 'Right! Right!' She stopped driving as she felt unsafe in the car and was now unable to use the lawn mower or collect her pension.

The successive MMSE scores document her cognitive decline (Fig. 2). At the time of the second examination the general neurological examination was normal but her pursuit eye movements were broken up. There were frequent myoclonic jerks in the hands and feet but no other involuntary movements. A pout reflex was present but there were no other primitive signs. She substituted body parts when miming the use of common objects and hesitated when asked to perform intransitive tasks (e.g. wave/salute). She, like her twin brother, was noted to stumble over her words and again this took the form of a stuttering in spontaneous speech. At the third examination the speech was worse but there was no significant change in the other signs.

A low amplitude alpha rhythm was noted on the EEG. An MRI scan showed minimal atrophy and a periventricular halo was noted. Occasional non-specific white matter lesions were also reported.

#### *Living unaffected*

*Case II.2.* Eldest non-affected male. Present age: 58 years.

This ambidextrous man left school without qualifications at the age of 15 years and worked as a lubricant technician. He took early retirement at the age of 55 years. He had pulmonary tuberculosis at the age of 18 years and recently an episode of inflammatory bowel disease. He experienced no problems with his memory and was normal neurologically with an MMSE of 30 out of 30. An MRI scan, PET scan and neuropsychological assessment were normal.

#### *Neuropsychological tests administered*

*WAIS-R (Wechlser, 1981).* A shortened version was administered. Verbal and performance IQs are pro-rated from scores on the Digit Span, Vocabulary, Arithmetic and Similarities subtests and performance IQ is pro-rated from scores on the Picture Completion, Picture Arrangement and Block Design subtests.

*National Adult Reading Test (Nelson and Willison, 1991).* This test, consisting of 50 irregular words is administered to obtain a measure of reading skills and to provide an estimate of premorbid intelligence or optimal level of functioning in mildly affected and normal subjects, respectively. The raw scores were transformed into full scale IQ equivalents, according to the standard administration.

*Recognition Memory Test (Warrington, 1984).* The verbal version of this test consists of 50 stimulus words. Recognition memory is tested by presenting each of the words paired with a distractor. The subject was 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 is asked to recognize them when individually paired with a distractor photograph drawn from a similar pool. The raw scores were converted into age corrected percentile scores.

*Graded Naming Test (McKenna and Warrington, 1983).* This object naming test of graded difficulty consists of 30 black-and-white line drawings which subjects have to name. The number of objects correctly named was converted into an equivalent vocabulary percentile score.

*Oldfield picture naming (Oldfield and Wingfield, 1965).* This unstandardized object naming test consists of 30 line drawings of objects, including six very common items, which subjects have to name. The raw score was converted into a percentile score.

*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 any answer is deemed incorrect. The raw score was converted into a percentile score.

*Spelling test (Baxter and Warrington, 1994).* This oral spelling test consists of 30 irregularly spelt words, graded in difficulty. The raw scores was coverted into percentile scores.

*Visual Object and Space Perception Battery (Warrington and James, 1991).* The silhouettes subtest consists of 15 animal and 15 object stimuli. This graded difficulty test comprises 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 3D arrangement of square bricks. Subjects have to count the number of cubes in the structures. Both these subtests' raw scores were converted to percentile scores.

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

*Weigl Colour-Form Sorting task (Weigl, 1941).* This sorting task consists of 12 shapes; three circles, three triangles and three squares. Each shape is represented in one of four colours. The subject has to sort the items once according to each category: shape and colour. Standard instructions were given.

*Wisconsin Card Sorting Test (modified) (Nelson, 1976).* This sorting task consists of cards on which different numbers and colours of four different shapes appear. The category in which the cards are sorted is determined by the examiner and changes after every six cards that are correctly positioned by the subject. Numbers of errors are recorded along with the number of repeated wrong answers—perseverations. The result is recorded as a pass or fail.