Clinical phenotype and genetic associations in autosomal dominant familial Alzheimer's disease: a case series

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Summary

Background The causes of phenotypic heterogeneity in familial Alzheimer's disease with autosomal dominant inheritance are not well understood. We aimed to characterise clinical phenotypes and genetic associations with *APP* and *PSEN1* mutations in symptomatic autosomal dominant familial Alzheimer's disease (ADAD).

Methods We retrospectively analysed genotypic and phenotypic data (age at symptom onset, initial cognitive or behavioural symptoms, and presence of myoclonus, seizures, pyramidal signs, extrapyramidal signs, and cerebellar signs) from all individuals with ADAD due to *APP* or *PSEN1* mutations seen at the Dementia Research Centre in London, UK. We examined the frequency of presenting symptoms and additional neurological features, investigated associations with age at symptom onset, *APOE* genotype, and mutation position, and explored phenotypic differences between *APP* and *PSEN1* mutation carriers. The proportion of individuals presenting with various symptoms was analysed with descriptive statistics, stratified by mutation type.

Findings Between July 1, 1987, and Oct 31, 2015, age at onset was recorded for 213 patients (168 with *PSEN1* mutations and 45 with *APP* mutations), with detailed history and neurological examination findings available for 121 (85 with *PSEN1* mutations and 36 with *APP* mutations). We identified 38 different *PSEN1* mutations (four novel) and six *APP* mutations (one novel). Age at onset differed by mutation, with a younger onset for individuals with *PSEN1* mutations than for those with *APP* mutations (mean age 43·6 years [SD 7·2] *vs* 50·4 years [SD 5·2], respectively, p<0·0001); within the *PSEN1* group, 72% of age at onset variance was explained by the specific mutation. A cluster of five mutations with particularly early onset (mean age at onset <40 years) involving PSEN1's first hydrophilic loop suggests critical functional importance of this region. 71 (84%) individuals with *PSEN1* mutations and 35 (97%) with *APP* mutations presented with amnestic symptoms, making atypical cognitive presentations significantly more common in *PSEN1* mutation carriers (n=14; p=0·037). Myoclonus and seizures were the most common additional neurological features; individuals with myoclonus (40 [47%] with *PSEN1* mutations and 12 [33%] with *APP* mutations) were significantly more likely to develop seizures (p=0·001 for *PSEN1*; p=0·036 for *APP*), which affected around a quarter of the patients in each group (20 [24%] and nine [25%], respectively). A number of patients with *PSEN1* mutations had pyramidal (21 [25%]), extrapyramidal (12 [14%]), or cerebellar (three [4%]) signs.

Interpretation ADAD phenotypes are heterogeneous, with both age at onset and clinical features being influenced by mutation position as well as causative gene. This highlights the importance of considering genetic testing in young patients with dementia and additional neurological features in order to appropriately diagnose and treat their symptoms, and of examining different mutation types separately in future research.

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Introduction

Alzheimer's disease is the most common cause of dementia. In fewer than 1% of patients, Alzheimer's disease is caused by autosomal dominant mutations in the presenilin 1 (*PSEN1*),[1] presenilin 2 (*PSEN2*),[2] or amyloid precursor protein (*APP*) genes.[3] Autosomal dominant familial Alzheimer's disease (ADAD) is considered to be clinically similar to sporadic disease (with the exception of younger age at onset) and both are characterised by progressive impairment of episodic memory. Although atypical phenotypes are seen in both familial and sporadic Alzheimer's disease,[4–6] relatively little is known about the proportion of individuals with ADAD who present with atypical cognitive symptoms, the prevalence of additional neurological features, or the relationships between genotype, phenotype, and the pathophysiological mechanisms that might underlie them.

Prevention trials for ADAD are underway and have stimulated research into biomarker changes in preclinical Alzheimer's disease. However, these trials also necessitate better understanding of the natural history of Alzheimer's disease in the symptomatic phase and of factors that influence age at onset. A recent meta-analysis found that mutation type accounted for a large proportion of the variance in age at onset, but substantial variation was still observed between, and even within,

Research in context

Evidence before this study

We searched PubMed for reports on the clinical phenotype of autosomal dominant familial Alzheimer's disease (ADAD) up to April 23, 2016, using the following search terms: "familial Alzheimer's disease", "autosomal dominant Alzheimer disease", "presenilin", "PSEN1", "PSEN2", and "APP", with no language restrictions. We identified 200 publications reporting clinical information on individuals with ADAD, mostly from single pedigrees or small case series. We found 22 reviews of this literature, although the results of such reviews could potentially be subject to the publication bias caused by reporting atypical phenotypes more frequently than typical presentations. Therefore, while it is clear from the literature that atypical phenotypes occur in ADAD, less is known about the frequency of their occurrence, correlations between genotype and phenotype, and the pathophysiological mechanisms that might underlie them.

Added value of this study

We investigated the clinical phenotypes of ADAD in a large UK case series, including patient data collected since identification of the first mutation over 25 years ago. We ascertained the frequency of presenting cognitive symptoms and additional neurological features, and investigated their associations with age at symptom onset, *APOE* ε4 genotype, and mutation position. 44 different mutations in the *PSEN1* or *APP* genes were present in the cohort, including five novel variants that are reported here for the first time. We found clinically important phenotypic differences between patients with *APP* mutations and those with *PSEN1* mutations. In addition to their younger age at symptom onset, *PSEN1* mutation carriers more frequently presented with atypical cognitive symptoms and additional neurological features. Exploration of heterogeneity of clinical presentations between different *PSEN1* mutations suggested that mutation position might influence phenotype. Atypical cognitive presentations and spastic paraparesis were associated with *PSEN1* mutations beyond codon 200, particularly involving exon 8. Conversely, particularly early ages at onset were observed for a cluster of mutations before codon 200 involving the first hydrophilic loop of PSEN1.

Implications of all the available evidence

In describing the wide clinical spectrum of ADAD presentation, we highlight the importance for clinicians of considering genetic testing in young patients with dementia and additional neurological features, particularly when there is a family history of Alzheimer's disease or when the family history is not available. Appreciation of atypical ADAD phenotypes is important from a diagnostic perspective and might also offer insights into the mechanisms by which different mutations cause disease. In view of the phenotypic heterogeneity that exists within ADAD, particularly between *APP* and *PSEN1* mutation carriers, it could be informative to examine different mutation types separately in observational studies and clinical trials of patients with ADAD.

families with the same mutation.[7] Some studies of families with *APP*, *PSEN1*, or *PSEN2* mutations[8–10] have reported younger age at onset in *APOE* ε4 carriers, although this association was not evident in a 2014 meta-analysis.[7] Relatively little is known about the factors underlying variability in age at onset for different mutations within a single gene, although *PSEN1* mutations beyond codon 200 have been associated with a later onset, more severe amyloid angiopathy, and a greater burden of white matter hyperintensities on MRI than mutations before codon 200.[5,11,12]

We aimed to analyse the clinical phenotype (initial cognitive symptoms and the frequency of additional neurological features) of a large cohort of individuals with ADAD; investigate potential associations with age at symptom onset, mutation position, and *APOE* ε genotype; and report the clinical and neuropathological features of the individuals with novel mutations.

Methods

Participants

Between July 1, 1987, and Oct 31, 2015, families with histories suggestive of ADAD were referred to the Dementia Research Centre (DRC) at University College London's Institute of Neurology (London, UK) from clinical and research centres across the UK and Ireland. We used clinical and genetic data from these families (11 with *APP* mutations, 55 with *PSEN1* mutations) in this study. Five families with *APP* duplications have also been identified, but are not included in the analyses presented here because data have been reported elsewhere.[13] We did not include individuals with sequence variants of questionable pathogenicity in this study.

Ethical approval for the study was provided by The National Hospital for Neurology and Neurosurgery and Institute of Neurology Joint Research Ethics Committee (subsequently the National Research Ethics Service Committee, London Queen Square). Written informed consent was obtained from all participants or from their guardian if cognitive impairment prohibited written informed consent.

Procedures

NSR evaluated contemporaneous records to determine age at symptom onset—defined as the age at which progressive symptoms of cognitive, behavioural, or motor changes were first noticed by someone who knew the patient well—the initial cognitive or behavioural symptoms, and the presence of the following neurological features: myoclonus, seizures, pyramidal signs (such as

spastic paraparesis), extrapyramidal signs (such as rigidity), and cerebellar signs (such as ataxia). We classified neurological features as early (≤5 years from symptom onset) or late (>5 years from onset). *APOE* ε4 status was determined by the Medical Research Council (MRC) Prion Unit (London, UK) using minor groove binding probe genotyping assays (TaqMan, Applied Biosystems).

Mutation analysis was carried out as described previously.[14] The likely pathogenicity of novel variants was predicted using a previously published algorithm,[15] and the tools PolyPhen (version 1.1.3) and PROVEAN (version 2). We assessed individuals with novel variants in *PSEN1* or *APP* for the presence of additional mutations in other dementia-related genes using the MRC Dementia Gene Panel (appendix).[16] Where possible, when a novel sequence variant was found in the proband, other affected family members were genotyped by sequencing the relevant exon to demonstrate cosegregation between the mutation and disease.

See Online for appendix

Two individuals with novel variants underwent post-mortem brain donation to the Queen Square Brain Bank at the UCL Institute of Neurology. We assessed amyloid β-positive plaque pathology using the Consortium to Establish a Registry for Alzheimer's Disease recommendations[17] and neurofibrillary tangle pathology with Braak staging.[18]

Statistical analysis

We investigated differences in age at symptom onset between the *APP* and *PSEN1* mutation groups, and between *APOE* ε4 carriers and non-carriers within each genetic group, using two-sample *t* tests. We analysed associations between age at onset and *PSEN1* mutation using a linear mixed effects model with random effects for mutation and family. The intraclass correlation coefficient (ICC) was used to quantify the proportion of variance in age at onset explained by mutation, and by mutation and family. We analysed groups of individuals with *APP* and *PSEN1* mutations separately to calculate the proportion of individuals presenting with amnestic symptoms or with atypical symptoms of behavioural change, language impairment, dyscalculia, or executive impairment; and the proportions with myoclonus, seizures, and pyramidal, extrapyramidal or cerebellar signs. We used two-sample *t* tests to investigate whether age at onset differed between individuals with typical

	Exon	Number of families	Number of affected individuals in the family (range)	Mean age at onset, years (range)
APP				
p.Ala692Gly	17	1	4	46 (39–54)
p.Val715Ala	17	1	1	42
p.Val717Gly	17	1	13	50 (40–59)
p.Val717Ile	17	6	22 (1–8)	52 (39–59)
p.Val717Leu	17	1	4	49 (48–51)
p.Thr719Asn	17	1	1	46
PSEN1				
Intron 4 (g.23024delG)	4	4	17 (1–12)	38 (35–45)
p.Tyr115Cys	5	2	2	39 (34–44)
p.Tyr115His	5	1	4	34 (30–36)
p.Thr116Asn	5	1	2	34
p.Glu120Lys	5	2	7 (2–5)	35 (31–39)
p.Ser132Ala	5	1	3	59 (58–60)
p.Met139Val	5	4	18 (1–9)	40 (35–48)
p.Ile143Phe	5	1	2	56 (53–59)
p.Met146Ile	5	2	6 (2–4)	48 (43–50)
p.Leu153Val	5	1	3	35 (35–36)
p.Tyr154Cys	5	1	1	41
p.Leu166Arg	6	1	1	40
p.Leu166del	6	1	1	38
ΔI167 (p.Ile168del)	6	1	5	54 (43–60)
p.Leu171Pro	6	1	5	42 (40–43)
p.Glu184Asp	7	3	5 (1–2)	40 (37–45)
p.Ile202Phe	7	1	2	48 (47–48)
p.Gln222Pro	7	1	1	45
p.Gly206Val	7	1	1	30
p.Ile229Phe	7	1	3	33 (32–34)
p.Leu235Val	7	1	4	52 (44–59)
p.Phe237Leu	7	1	1	47
p.Leu250Ser	7	1	7	52 (47–56)
p.Ala260Val	8	1	1	40
p.Cys263Phe	8	1	2	59 (58–59)
p.Pro264Leu	8	2	3 (1–2)	50 (44–56)
p.Pro267Ser	8	1	2	38
p.Arg269His	8	3	4 (1–2)	55 (50–62)
p.Arg278Ile	8	1	7	51 (44–59)
p.Glu280Gly	8	3	16 (1–8)	42 (39–49)
p.Phe283Leu	8	1	15	46 (42–48)
p.Ser290Cys	9	1	5	42 (41–44)
ΔE9*	9	1	1	45
p.Arg377Met	11	1	1	38
p.Gly378Val	11	1	5	44 (41–48)
p.Gly394Val	11	1	1	40
p.Pro436Ser	12	1	3	46 (44–50)
p.Thr291Ala and p.Ala434Thr	9 and 12†	1	1	42

Sex-specific information was not recorded during evaluation of patient medical histories. *The exon 9 deletion (NM_000021.3:c.869-1G→T; p.Ser290Cys; Thr291_Ser319del) is commonly referred to as ΔE9. †One patient had both Thr291Ala on exon 9 and Ala434Thr on exon 12.

***Table 1*: Mutations carried by the patients in the cohort**

presentations and those with atypical presentations and between individuals with and without each additional neurological feature. Fisher's exact tests were used to investigate associations between atypical cognitive presentations or additional neurological features and *APOE* ε4 status, *PSEN1* exon, and *PSEN1* mutation location (compared with codon 200). We used a p value of less than 0·05 as our measure of statistical significance. We used Stata version 12 for all analyses.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Age at symptom onset was available for 213 individuals (168 with *PSEN1* mutations and 45 with *APP* mutations; table 1); *APOE* status could be established for 126 of these individuals (95 with *PSEN1* mutations and 31 with *APP* mutations). Onset was significantly later for individuals with *APP* mutations (mean age 50·4 years [SD 5·2]; range 39–59) than for those with *PSEN1* mutations (43·6 [7·2], range 30–62; p<0·0001). Possession of an *APOE* ε4 allele was not associated with age at onset for individuals with *PSEN1* mutations (43·6 years [SD 7·2] for *APOE ε4* positive *vs* 42·3 years [6·7] for *APOE* ε4 negative; p=0·385) or for those with *APP* mutations (50·7 years [4·2] for *APOE* ε4 positive *vs* 50·7 years [5·3] for *APOE* ε4 negative; p=0·998).

In patients with a *PSEN1* mutation, age at onset was found to be influenced by the specific mutation, with 72% of the variance in age at onset explained by mutation (ICC 0·72). Mutation and family membership together explained 82% of the variance in age at onset (ICC 0·82). Individuals with mutations located before codon 200 had, on average, a younger age at onset (41·3 years [SD 7·2]) than did those with mutations beyond codon 200 (45·8 years [6·4], p<0·0001), which appeared to be driven by a younger age at onset for mutations involving exon 4 and 5 (figures 1, 2). Age at onset for a patient with two *PSEN1* substitutions (p.Thr291Ala and p.Ala434Thr) was excluded from our analyses because it was unclear whether pathogenicity was due to one or both of these aminoacid substitutions. The intron 4 (NM_000021.3:c.338+1delG) mutation was classified as involving exon 4 because it is located just outside this exon (appendix).[20]

Detailed contemporaneous records documenting medical history and neurological examination findings were available for 121 of 213 individuals (85 with *PSEN1* mutations and 36 with *APP* mutations), and *APOE* ε4 genotype could be established for 101 of these individuals (71 *PSEN1* and 30 *APP*). 35 of the 36 individuals with *APP* mutations presented with typical amnestic

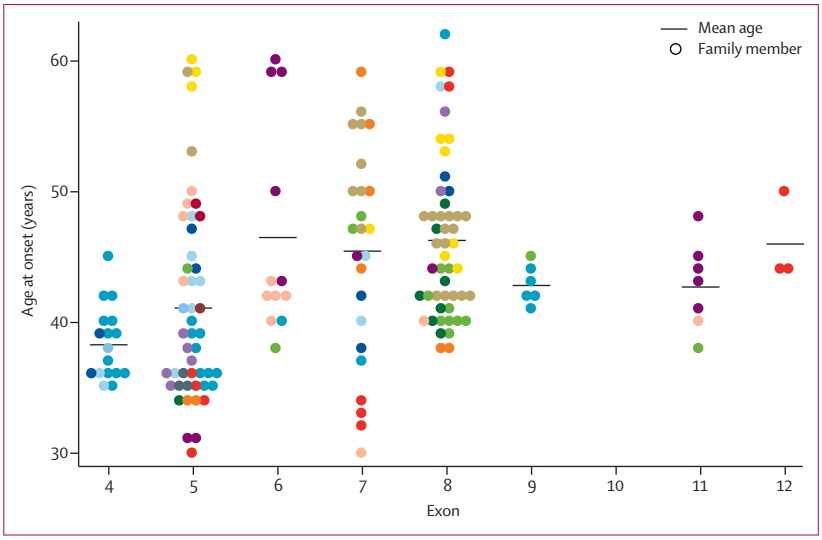

Figure 1: **Age at onset for our cohort of *PSEN1* mutation carriers**
Each dot represents one individual's age at onset. Within each exon, different colours represent separate families; multiple families with the same mutation are indicated by different shades of the same colour (blue, green, purple, or pink). Bars indicate mean age at onset for mutations involving each exon.

symptoms; the other patient presented with dyscalculia but developed memory problems soon after (table 2). Of the 85 individuals with *PSEN1* mutations, 71 (84%) presented with amnestic symptoms and 14 (16%) with atypical cognitive presentations, which were more frequently associated with *PSEN1* than *APP* mutations (p=0·037). Of the 14 *PSEN1* mutation carriers with atypical initial cognitive features, seven (8%) presented with behavioural change, three (4%) with language impairment, two (2%) with dyscalculia, and two (2%) with a dysexecutive syndrome (table 2). The *PSEN1* subgroup with atypical cognitive presentations had, on average, a somewhat older age at onset than those with typical amnestic symptoms (46·2 years [SD 5·9] *vs* 42·0 years [7·4], p=0·046). Prevalence of atypical cognitive presentations differed markedly between exons, occurring in ten (45%) of 22 individuals with exon 8 mutations, and fewer than 20% of individuals with mutations involving other exons (appendix). As a result, atypical presentations were significantly more common in individuals whose mutation was located after codon 200 (p=0·006). There was no association between atypical cognitive symptoms and *APOE* ε4 status (data not shown).

In the *APP* group, myoclonus and seizures were the only additional neurological features observed, and the frequency of myoclonus and seizures did not differ significantly between the *PSEN1* and *APP* groups. In the *APP* group, 12 (33%) carriers had myoclonus and nine (25%) developed seizures. Of the 12 individuals with myoclonus, onset of myoclonus was early (≤5 years from onset) in five (42%), late in two (17%), and uncertain in five (42%). Of the nine individuals with seizures, onset was early in three (33%), late in three (33%), and uncertain in three (33%). In the *PSEN1* group, 40 (47%)

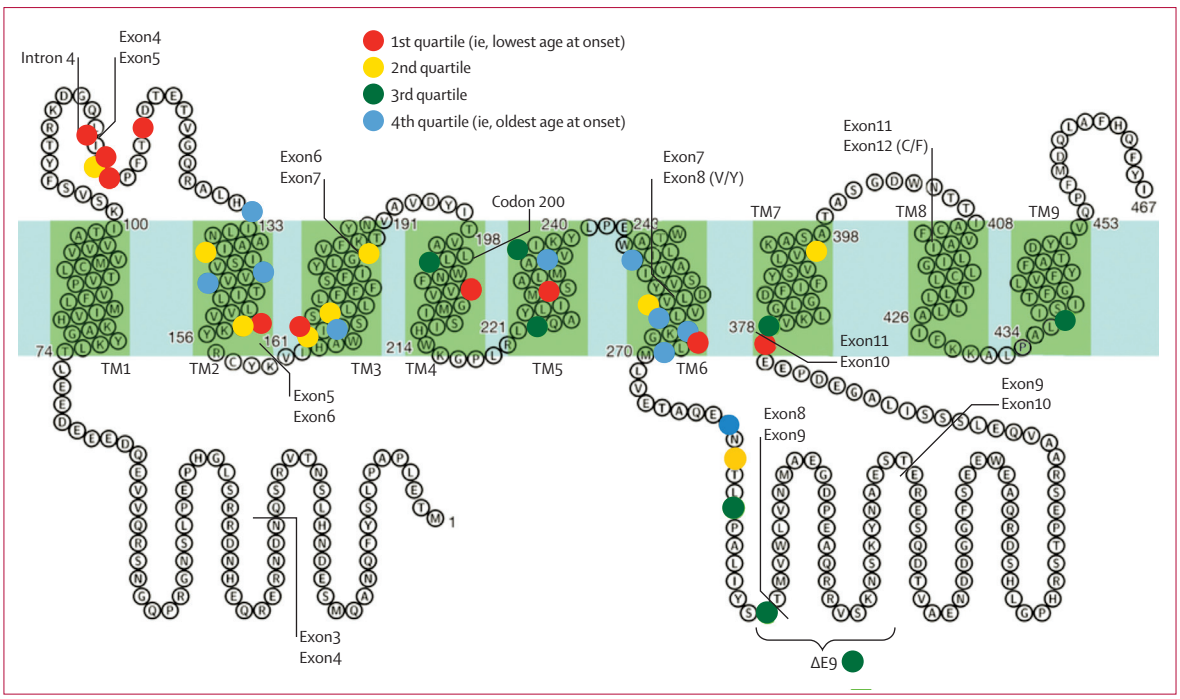

Figure 2: **Location of the mutations present in our cohort of *PSEN1* mutation carriers, shown according to age-at-onset quartiles**
Predicted membrane topology of PSEN1, with the nine transmembrane domains (dark green shaded boxes) and boundaries between coding exons indicated. The sites of aminoacid substitution (or insertion in the case of intron 4, and deletion in the case of ΔE9) are indicated by coloured circles, with the colour representing the quartile that the mean age at onset for that mutation falls within. Adapted by permission from Macmillan Publishers: *Nature* (2012).[19] Codon 200 is shown within the fourth transmembranal domain of the protein. TM=transmembrane domain.

of 85 carriers had myoclonus and 20 (24%) had seizures. Of the 40 individuals with myoclonus, onset of myoclonus was early in 28 (70%), late in nine (23%), and uncertain in three (7%). Of the 20 individuals with seizures, onset was early in six (30%), late in 10 (50%), and uncertain in four (20%). Individuals with myoclonus were significantly more likely to develop seizures: 16 (40%) developed seizures in the *PSEN1* group (p=0·001) and six (50%) in the *APP* group (p=0·036). There was no association between myoclonus or seizures and age at onset or *APOE* ε4 status in either the *APP* or *PSEN1* groups. There was no association between seizures or myoclonus and *APOE* ε4 status, exon or mutation location with respect to codon 200 in the *PSEN1* group (appendix).

Pyramidal, extrapyramidal and cerebellar signs were only seen in patients with *PSEN1* mutations (table 2, appendix). Pyramidal signs were observed in 21 (25%) of the 85 *PSEN1* carriers. All of these individuals had spastic paraparesis, and 18 also had upper limb pyramidal signs. Of the 21 patients with pyramidal signs, 15 (71%) developed them early, although none were reported to have these signs before onset of cognitive symptoms. The remaining six (29%) patients developed them late, with an absence of pyramidal signs at earlier assessments. There were no associations between pyramidal signs and age at onset in the *PSEN1* cohort as a whole, and insufficient numbers to investigate such associations at the level of individual families or mutations. Pyramidal signs were, however, observed more frequently in association with *PSEN1* mutations after codon 200 than before codon 200 (p=0·024), with particularly high frequency (50%) in patients with mutations on exon 8 (appendix).

Extrapyramidal signs were observed in 12 (14%) of the 85 *PSEN1* mutation carriers, occurring early in eight (67%), late in three (25%), and of uncertain onset in one (8%). No associations were found with age at onset, *APOE* ε4 status, or exon or *PSEN1* mutation location (compared with codon 200). One of the patients with early extrapyramidal signs (*PSEN1* p.Tyr115His) had markedly asymmetrical features consistent with a corticobasal syndrome (appendix).

Cerebellar signs were observed in three (4%) of the 85 *PSEN1* mutation carriers, occurring early in two, and late in one. No associations were found with age at onset, *APOE* ε4 status, or exon or *PSEN1* mutation location (compared with codon 200).

We identified four novel mutations in *PSEN1* and one novel mutation in *APP*. The novel variants in *APP* (p.Thr719Asn [NM_000484·3:c.2156C→A]) and *PSEN1* (p.Gln222Pro [NM_000021.3:c.665A→C], p.Phe283Leu [NM_000021.3:c.849T→G]) were identified in three patients with typical amnestic presentations. Two *PSEN1* substitutions (p.Ala434Thr [NM_000021.3:c.1301G→A] and the novel p.Thr291Ala [NM_000021.3:c.871A→G] variant) were identified in a patient who presented with memory symptoms, parkinsonism, and pyramidal signs

and who had Alzheimer's disease pathology with cotton wool plaques, diffuse deposits, and severe amyloid angiopathy post mortem (figure 3, appendix). The fifth

	Patients with the phenotype (n/N)
Behavioural presentation	
PSEN1	
p.Met139Val	1/14
p.Leu166Arg	1/1
p.Pro264Leu	2/3
p.Arg269His	1/2
p.Arg278Ile	1/5
p.Glu280Gly	1/9
Language presentation	
PSEN1	
p.Pro264Leu	1/3[21]
p.Arg278Ile	2/5[22]
Dycalculia presentation	
PSEN1	
Intron 4 (g.23024delG)	1/9
p.Leu235Val	1/2
APP	
p.Val717Ile	1/19
Dysexecutive presentation	
PSEN1	
p.Glu280Gly	2/9
Myoclonus	
PSEN1	
Intron 4 (g.23024delG)	6/9
p.Tyr115Cys	1/1
p.Tyr115His	1/2
p.Ser132Ala	1/1
p.Met139Val	10/14[23,24]
p.Met146Ile	2/3
p.Glu184Asp	1/3
p.Ile202Phe	1/1[25]
p.Gly206Val	1/1
p.Ile229Phe	1/1
p.Phe237Leu	1/1
p.Leu250Ser	1/1
p.Ala260Val	1/1
p.Pro264Leu	1/3
p.Arg269His	1/2
p.Arg278Ile	3/5
p.Glu280Gly	4/9
p.Ser290Cys	1/2
p.Gly278Val	1/1
p.Gly394Val	1/1
APP	
p.Val717Gly	5/11[26]
p.Val717Ile	5/19
p.Val717Leu	1/4
p.Thr719Asn	1/1

(Table 2 continues in next column)

	Patients with the phenotype (n/N)
(Continued from previous column)	
Seizures	
PSEN1	
Intron 4 (g.23024delG)	5/9
p.Tyr115Cys	1/1
p.Tyr115His	1/4
p.Met139Val	4/14[23,24]
p.Met146Ile	2/3
p.Gly206Val	1/1
p.Ala260Val	1/1
p.Pro264Leu	2/3
p.Pro267Ser	1/1
p.Glu280Gly	2/9
APP	
p.Ala692Gly	1/1
p.Val717Gly	5/11[26]
p.Val717Ile	2/19
p.Val7171Leu	1/4
Spastic paraparesis with or without other pyramidal signs	
PSEN1	
Intron 4 (g.23024delG)	1/9
p.Tyr115His	1/2
p.Glu120Lys	1/3
p.Met139Val	1/14
p.Met146Ile	1/3
p.Leu166Arg	1/1
p.Glu184Asp	1/3
p.Pro264Leu	1/3
p.Arg278Ile	2/5
p.Glu280Gly	8/9[27]
p.Gly394Val	1/1
p.Thr291Ala and p.Ala434Thr	1/1
ΔE9	1/1
Extrapyramidal signs	
PSEN1	
p.Tyr115His	1/3
p.Glu120Lys	1/3
p.Ser132Ala	1/1
p.Met146Ile	1/3
p.Leu166Arg	1/1
Δ167 (p.Ile168del)	1/2
p.Arg278Ile	3/5
p.Glu280Gly	2/9
p.Thr291Ala and p.Ala434Thr	1/1
Cerebellar signs	
PSEN1	
p.Tyr115Cys	1/1
p.Glu280Gly	1/9[27]
p.Ser290Cys	1/2

References have been provided where clinical phenotype data from some individuals have been reported in previous publications.

Table 2: **Prevalence of phenotypes and neurological features in individuals with *APP* or *PSEN1* mutations**

individual with a novel variant (*PSEN1* p.Ser132Ala [NM_000021.3:c.394T→G]) presented with a dementia with Lewy bodies phenotype and had Alzheimer's disease pathology with severe neocortical Lewy body disease identified post mortem. (figure 4). This patient also had an intronic variant (NM_005910·5: rs11872014) in the *MAPT* gene. Although there is no consensus on the impact of the variant on *MAPT* splicing, given that this *MAPT* variant has been found in an elderly healthy control (unpublished data, MRC Prion Unit) and described 321 times in the Exome Aggregate Consortium (ExAC) dataset with an allele frequency of 0·002952 (0·004401 in Europeans), it is unlikely to have caused disease in this patient. No additional variants in dementia-related genes were found in the other individuals with novel *PSEN1* or *APP* variants using the MRC Dementia Gene Panel.[16] All novel sequence variants identified were absent from 100 healthy, white control participants who were unrelated to these patients. With the exception of p.Ser132Ala, which was seen in one individual of European ancestry, none of the variants were found in the ExAC dataset. We discuss the likely pathogenicity of the novel variants and provide further clinical and neuropathological details in the appendix.

For the **Exome Aggregate Consortium (ExAC) dataset** see http://exac.broadinstitute.org

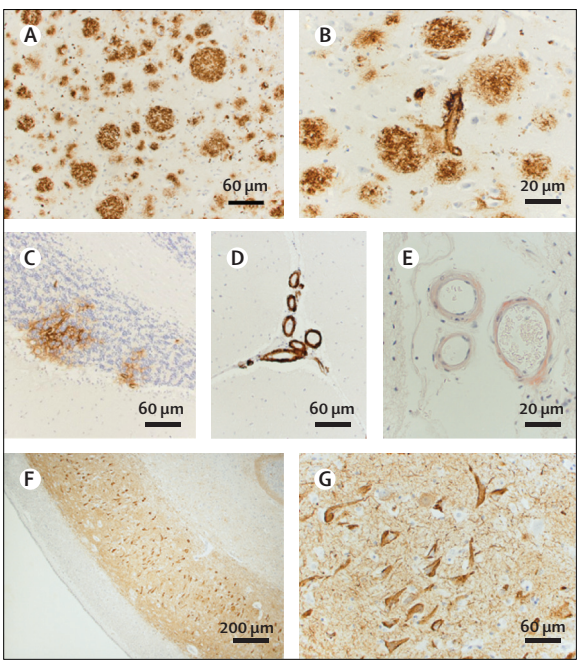

Figure 3: **Neuropathological findings in a 42-year-old man with a *PSEN1* double substitution (p.Thr291Ala and p.Ala434Thr), presenting with cognitive impairment and pyramidal and extrapyramidal signs**
Amyloid pathology in the hippocampus of cotton wool plaques (A) and capillary cerebral amyloid angiopathy (B). Diffuse deposits shown in the granule cell layer of the cerebellum (C). Amyloid β deposits in the leptomeningeal blood vessels (D). Amyloid β deposits are shown to be in an amyloid conformational state using Congo red staining (E). AT8 immunoreactivity for abnormally phosphorylated tau in the CA1 subregion of the hippocampus (F), and at 40X magnification (G) detailing the neurofibrillary tangles and neuropil threads.

Discussion

Clinically significant differences are present between *PSEN1* and *APP* mutation carriers with ADAD, emphasising the potential importance of examining these groups separately in observational research and clinical trials. In addition to the younger age at symptom onset for individuals with *PSEN1* mutations than in those with *APP* mutations, *PSEN1* mutation carriers more frequently presented with atypical cognitive symptoms and additional neurological features. Behavioural, language, and dysexecutive presentations, spastic paraparesis, and other pyramidal, extrapyramidal, and cerebellar signs were only seen in the individuals with *PSEN1* mutations. By contrast, myoclonus and seizures affected a similar proportion of patients with *APP* and *PSEN1* mutations. In both genetic groups, individuals with myoclonus were more likely to develop seizures than were those without myoclonus. These findings highlight the need for clinicians to be vigilant of symptoms of seizure activity when myoclonus is present.

Limitations of our study are that some atypical phenotypes, such as movement disorder presentations or much older onset, might not have been seen in our case series due to our centre being more likely to get referrals for younger patients with cognitive symptoms. Also, not all patients were followed to advanced stages of illness, so late neurological features might be more frequent than we describe here. With enrolment of individuals over a long period of time, there is the potential for families to have greater awareness and therefore earlier recognition of symptom onset with successive generations. The relative non-diversity of individuals seen in a single country might also limit generalisability of the findings. However, the mean age at onset in our cohort was very similar to that in a French case series[28] and in recent systematic reviews of ADAD.[5,7,28] As in our case series, spastic paraparesis and extrapyramidal and cerebellar signs were seen in French *PSEN1* mutation carriers, but not *APP* mutation carriers, usually manifesting within 5 years of symptom onset. The proportion of French patients with *PSEN1* mutations presenting with frontal symptoms (11%) was also similar to the combined proportion of individuals in our series whose initial cognitive symptoms were behavioural (8%) or dysexecutive (2%).[28] Finally, a non-amnestic presentation has been reported in 16% of individuals with ADAD worldwide;[5] which is the same proportion as in individuals with *PSEN1* mutation carriers in our cohort.

While some of the *PSEN1* mutation carriers in our study presented with non-amnestic cognitive symptoms, all but one of the *APP* mutation carriers had initial memory symptoms. These phenotypic differences have some support from neuroimaging studies: we have previously reported that *APP* mutation carriers have greater hippocampal atrophy than *PSEN1* mutation

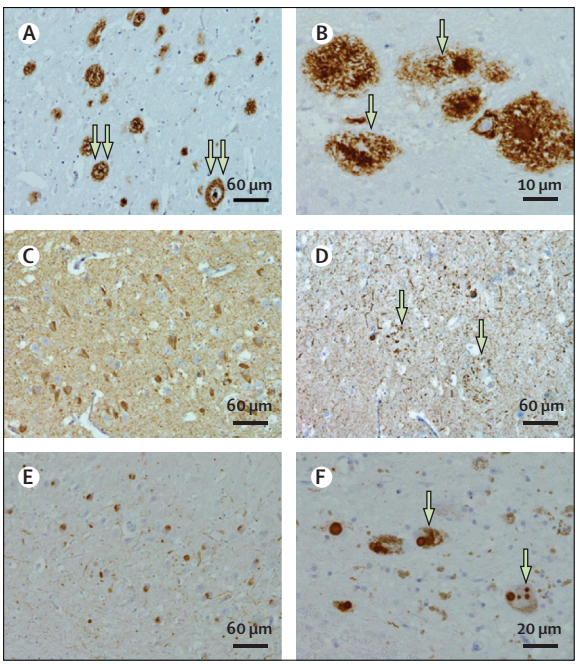

Figure 4: **Neuropathological findings in a 70-year-old man with the novel *PSEN1* p.Ser132Ala mutation presenting with a dementia with Lewy bodies phenotype**

Amyloid pathology in the hippocampus of cored amyloid plaques (A; double arrows), and diffuse amyloid β (B; arrows). AT8 immunoreactivity for abnormally phosphorylated tau of neurofibrillary tangles in the CA1 subregion of the hippocampus (C), and of neuritic plaques in the temporal cortex (D; arrows). α-synuclein immunohistochemistry of Lewy neurites and Lewy bodies in the CA1 sub-region of the hippocampus (E), and Lewy bodies found in the dopaminergic neurons of the substantia nigra (F; arrows).

carriers of similar disease severity, whereas *PSEN1* mutation carriers show more extensive neocortical atrophy and white matter involvement; the latter could underlie some of the atypical features observed in the *PSEN1* group.[29] PSEN1 forms the catalytic subunit of gamma-secretase, which processes APP, but also a large number of other substrates involved in various physiological functions, including myelin repair and vascular and immune function. Gamma-secretase carries out an initial endopeptidase cleavage of its substrates, followed by successive carboxypeptidase-like cleavages. *PSEN1* mutations all appear to decrease the efficiency of this carboxypeptidase-like activity, resulting in the release of longer amyloid β peptides, which are more prone to aggregation. Most *PSEN1* mutations also affect the endopeptidase activity, but to various degrees, potentially affecting the processing of other substrates in addition to APP.[30,31] We speculate that altered processing of other substrates could contribute to the atypical phenotypes witnessed in association with some *PSEN1* mutations. Supporting this notion, atypical cognitive presentations and pyramidal signs in participants of this study were seen more frequently in association with *PSEN1* mutations involving exon 8. The residues encoded by exon 8 lie within the hydrophilic sequence between transmembrane domains six and seven of PSEN1, which is where the cleavage site processed by autocatalytic activity resides.[32] Furthermore, patients with two atypical phenotypes—corticobasal syndrome (p.Tyr115His) or dementia with Lewy bodies (p.Ser132Ala) presentations—had mutations involving hydrophilic loop 1, which has been proposed to form the initial substrate binding site in PSEN1, with Ser132 playing a crucial role.[33] Indeed, the p.Tyr115His mutation has been found to reduce endopeptidase efficiency due to substantially decreased affinity for the Notch substrate, while the affinity for APP is affected to a lesser extent.[30] Certain mutations might therefore differentially affect the substrate specificity of the gamma-secretase complex and investigating whether this mechanism contributes to atypical clinical phenotypes is an important direction for future work. It was notable that the patient with the *PSEN1* p.Ser132Ala mutation, who presented with a dementia with Lewy bodies phenotype, had severe neocortical Lewy body pathology. However, concomitant Lewy body pathology is a frequent finding in ADAD.[34] Large cohort studies will be important to further investigate clinical phenotype and clinicopathologic correlations in ADAD, ideally with unaffected family members acting as controls.

Our results suggest that multiple factors could contribute to phenotypic heterogeneity in ADAD. There was sometimes considerable variability in the clinical features of individuals with the same mutation, even within a single family. Even so, we found that mutations before codon 200 were associated with younger age at onset, whereas mutations beyond codon 200 were more frequently associated with later ages at onset, atypical cognitive presentations, and pyramidal signs. Given the relatively small numbers of patients manifesting each atypical feature, and the numbers of associations (although not independent), it is important to be cautious about nominally significant associations. Nonetheless, we felt it important to report them to allow replication in other cohorts. Indeed, a 2015 systematic review[5] also reported that *PSEN1* mutations before codon 200 had younger ages at onset and were more frequently associated with seizures and myoclonus, whereas mutations beyond codon 200 were more frequently associated with spastic paraparesis. Codon 200 is an arbitrary cut-off, and mapping the mean ages at onset for different mutations to the structure of PSEN1 (figure 2) suggests that there might be certain areas of the protein where mutations cause particularly early-onset disease, such as the first hydrophilic loop encoded by exons four and five. This extracellular loop contributes to a key allosteric core that changes amyloid β profiles through carboxypeptidase-like activity without affecting the endopeptidase function of gamma-secretase.[35,36] As qualitative changes in amyloid β profiles appear to underlie the pathogenicity of *PSEN1* mutations,[30,31] one could speculate that these might be more dramatically

altered by mutations involving this allosteric core, resulting in a more aggressive phenotype.

We have demonstrated that a subset of patients with ADAD do not have typical amnestic presentations. Because atypical presentations also occur in sporadic Alzheimer's disease, we do not think that our findings challenge the idea that familial cases represent a paradigm for Alzheimer's disease, but rather highlight the importance of distinguishing and investigating atypical phenotypes to understand the complex underlying mechanisms that might contribute to disease. The clinical features of *PSEN1*-associated ADAD could erroneously suggest a diagnosis of frontotemporal or vascular dementia, corticobasal degeneration, or dementia with Lewy bodies. We suggest that it is important to consider ADAD in the differential diagnosis of patients with early-onset dementia with additional neurological features. ADAD detection rates have, at least historically, been lower than expected based on genetic epidemiology data, and have shown considerable variability across different regions of the UK.[37] Failure to identify a mutation in these families might deprive the affected patient of a correct diagnosis and appropriate symptomatic treatment, and also has implications for the individual's family. Individuals at risk of ADAD should, if they wish, be given access to genetic counselling so that they can discuss their choices in a variety of areas, including predictive genetic testing and reproductive options such as preimplantation genetic diagnosis. They might benefit from the peer support of connecting with other families affected by ADAD,[38] and from opportunities to participate in research, including preclinical treatment trials aiming to delay or prevent the onset of symptoms.

Contributors

NSR, MNR, and NCF conceived of the study. NSR, PSJW, YL, MNR, and NCF contributed to recruitment and clinical assessment. JMN contributed to statistical analysis; TL, TR, and JH analysed the neuropathological data. RG, GA, JK, JB, LC-G, BdS, and SM contributed to genetic analysis or interpretation of the genotype and phenotype data. NSR drafted the initial version of the report, all authors contributed to revision and editing of the report.

Declaration of interests

NCF reports fees (all paid to University College London) for consultancy from Novartis, Sanofi, Roche/Genentech, and GlaxoSmithKline for contracted image analyses from Janssen Alzheimer's Immunotherapy, and for serving on a data monitoring committee from Aducanumab/Biogen. MNR reports fees (paid to University College London) for serving on a data monitoring committee for Servier. BdS reports grants and consultancy fees from Janssen Pharmaceutica, consultancy fees from FORUM Pharmaceutica and reMYND. Additionally, BdS has a patent pending for presenilin deficient multipotent cell lines and screening methods for g-secretase activities and modulators of g-secretase activities using these lines (EP 00200671.6), a patent pending for binding domains between presenilins and their substrates as targets for drug screening (EP 01201015.3), and a patent pending for peptides inhibiting specific cleaving activities of presenilins (EP 02078915.2). All other authors declare no competing interests.

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