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A novel presenilin mutation (M233V) causing very early onset Alzheimer's disease with Lewy bodies

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Abstract

Presenilin 1 mutations are the major cause of autosomal dominant Alzheimer's disease: here we identify a new missense mutation causing a methionine to valine change at codon 233. This codon is homologous to a pathogenic presenilin 2 mutation with the same base change (ATG to GTG) and amino acid change (M239V). This mutation causes disease with an exceptionally early onset age (~30 years) in which pathological examination shows extensive Lewy bodies as well as plaques and tangles.

Keywords: Alzheimer's disease; Genetics; Presenilins; Lewy bodies

Presenilin 1 mutations are the major cause of early onset, autosomal dominant Alzheimer's disease [18]. Approximately 80 mutations have been described [3] and these are all believed to lead to disease through the alteration of amyloid precursor protein (APP) processing such that more of the amyloidogenic peptide Aβ42 is produced [6,17]. Pathogenic presenilin mutations are scattered throughout the molecule. There is a predilection for the exon 8 region [14] and for the transmembrane (TM) domains [2,11].

A family with exceptionally early onset of Alzheimer's disease inherited as an autosomal dominant trait (Fig. 1) came to our attention. In this family, the presenting features have been between 28 and 34 years and the age at death has been between 34 and 37 years. The proband died at age 34, after an extremely rapid course involving predominantly extrapyramidal features and early seizures. The pathology of her case has previously been described as including high counts of neurofibrillary tangles and amyloid plaques throughout the cerebral neocortical areas examined including occasional plaques in the spinal cord. There was occasional diffuse amyloid plaques in the striatum with dense plaques and occasional neurofibrillary tangles being present in both the external and internal segments of the pallidum. There were many nigral and cortical Lewy bodies [15] (Fig. 2) and the presence of moderate to severe amyloid angiopathy in leptomeningeal, cerebral and cerebellar vessels.

DNA was extracted from blood and brain tissue. DNA sequencing of the proband, carried out as we have previously described [2] revealed an ATG to GTG mutation at codon 233 leading to a predicted methionine to valine change at this residue of PS 1 exon 7. This caused the loss of a Nla III restriction enzyme cut in the mutant allele. No other relatives were available in the family. This mutation was not present in 150 control chromosomes.

This finding is of interest for three reasons: first, and simply, as a documentation of a new mutation. This codon is homologous to a pathogenic presenilin 2 mutation with the same bases change (ATG to GTG) and amino acid change (M239V) [16]. Second; this mutation occurs to the same residue as two previous mutations, M233L and M233T. These mutations are in predicted TM domain 5 [1,9]. While mutations to this domain do not align along predicted helical faces [5], it is clear that mutations do cluster to particular residues in both presenilin 1 and 2. The other two reported mutations at codon 233 cause an age of

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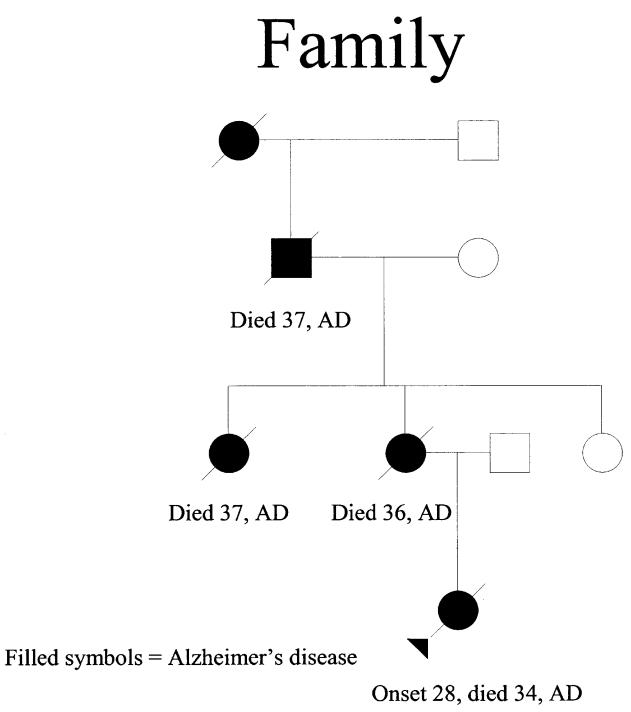

Fig. 1. The family tree: the mean age at onset of the family is 32 years (range 30–34). This pedigree and the pathology of the proband has been previously described in reference [15] as Pedigree 2.

onset of 46 years in one family (M233L) and in the other a very early age of onset of 35 years (M233T) with early seizures. In this TM domain there is no significant trend in age of onset, clinical or pathological features [3,8,12,13]. Third, the occurrence of Lewy bodies in this case confirm our and others' previous observations in cases with both APP and presenilin mutations that Lewy bodies are a significant pathological feature [4,6–8,10,12,13]. No detailed neuropathological details were available on the two other families with mutations at this residue to compare with our case. Lewy bodies have been identified in a number of different families with presenilin mutations in different TM domains but so far no correlations can be identified to link mutation position with neuropathology.

These data suggests that Lewy body formation is likely to be a downstream event from APP misprocessing [4–8] although the mechanism of their formation is as yet unknown. The occurrence of Lewy bodies in the brains of one so young can clearly not be an event unrelated to the pathological processes deriving from the presenilin mutation.

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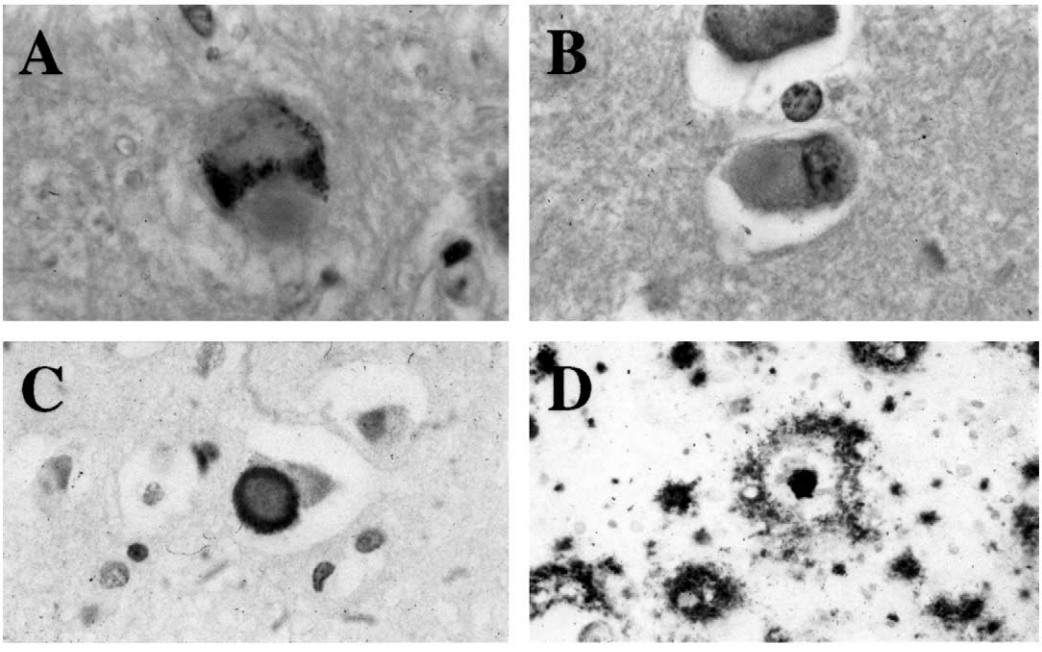

Fig. 2. (A) Nigral neuron with typical Lewy body. (B) Cortical Lewy body in the cingulum cortex. (C) Cortical Lewy body stained with an antibody to α-synuclein. (D) Numerous neocortical Aβ-positive senile plaques. (A and B: Haematoxylin and eosin, original magnification $\times$ 300; C: α-synuclein immunohistochemistry original magnification $\times$ 300; D: Aβ immunohistochemistry original magnification $\times$ 90).

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