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A novel mutation in the predicted TM2 domain of the presenilin 2 gene in a Spanish patient with late-onset Alzheimer's disease

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ABSTRACT

Mutations in the presenilin-2 (*PS-2*) gene are less frequent than mutations in the *PS-1* gene. All mutations described in the *PS-1* gene were found in early-onset Alzheimer's disease (AD) patients. At present, there are two missense mutations described for the *PS-2* gene in some AD pedigrees. We have therefore analyzed transmembrane 2 (TM2) and TM5 domains of the *PS-2* gene in AD patients and in a group of age-matched healthy controls. In a patient who was clinically diagnosed as having late-onset AD, we found a novel missense mutation consisting of a G->A substitution on exon *5* of the *PS-2* gene, which results in a Val to Ile substitution at codon 148 within the predicted TM2 domain of the PS-2 protein. This is the third mutation described in the *PS-2* gene and the first presenilin mutation detected in a Spanish AD patient. Both, the *N141I* mutation and the *V148I* mutation described here are located within the predicted TM2 domain and both were found in late-onset AD kindreds, whereas the mutation within the predicted TM5 domain was found in an early-onset AD pedigree. Carriers of mutations within TM2 of *PS-1* have a mean age at onset of 40 years, while the other mutations in *PS-1* occur in families with a mean age at onset of 47 years. In summary, we report here the first mutation in a presenilin gene in a Spanish AD case, which is the third mutation detected for the *PS-2* gene.

Key words Late-onset Alzheimer's disease · Presenilin-2 gene · TM2 domain · TM5 domain · Missense mutation

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INTRODUCTION

Since 1987, the genetic homogeneity of Alzheimer's disease (AD) has been disputed. AD is a genetic disorder which is heterogeneous in its etiology. To date genes on four chromosomes have been implicated in the etiopathogenesis of AD. Several missense mutations in the amyloid precursor protein gene (*APP*) on chromosome 21 have been found in about 3% of familial early-onset AD (EOAD), in which about 50% of relatives appear affected across several generations. This familial pattern is consistent with an autosomal dominant inheritance [1–8]. A vast majority of EOAD families have been related by linkage to the region 14q24.3 on chromosome 14 where the presenilin-1 gene (*PS-1*) was mapped [9–11]. Furthermore, a new locus segregating in some familial AD kindreds was found on chromosome 1 where the presenilin-2 gene (*PS-2*) was located [12, 13]. The protein product of *PS-1* shows a 67% homology with the protein encoded by *PS-2* [12–16].

Since 1995, when the *PS-1* gene at the chromosome 14 AD3 locus and *PS-2* on chromosome 1 at AD4 locus were first identified, genetic investigations in AD have concentrated on the identification of mutations affecting these genes. Many studies have also tried to establish how the abnormal *PS* gene products act in the pathogenesis of AD.

To date 33 missense mutations in 61 AD kindreds have been detected in the *PS-1* gene in addition to a point mutation upstream of a splice acceptor site which results in an in-frame deletion of exon *9* in several AD pedigrees, linked to chromosome 14 [14]. However, in the *PS-2* gene only two missense mutations have been identified in eight pedigrees [12, 13]. The *N141I* mutation within the transmembrane 2 (TM2) domain, consisting of a A->T substitution, was detected in seven Volga-German pedigrees with a disease onset from 44 to 75 years of age [12]. The *M239V* mutation within TM5 was described in an Italian pedigree (age at onset 50 years) and consists of a A->G substitution [13]. In

this study we have analyzed TM2 and TM5 domains of the *PS-2* gene in Spanish AD patients.

MATERIALS AND METHODS

We have analyzed TM2 and TM5 domains of the *PS-2* gene in AD patients ($n = 128$, age 66 ± 12.3 years, range 44–81 years), who were clinically diagnosed according to the American Psychiatric Association [17] and National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria [18], and in a group of age-matched healthy controls ($n = 95$, age 65 ± 11.2 years, range 40–82 years). DNA was purified from peripheral blood lymphocytes without phenol-chloroform extraction. We have designed a method in order to detect all possible mutations on TM2 and TM5 domains of the *PS-2* gene (Beyer et al., submitted for publication). A multiplex polymerase chain reaction (PCR) of these regions was carried out using primers previously described [12, 13]. PCR products were visualized by agarose gel electrophoresis in order to discard possible large deletions affecting all or parts of these regions. We developed a single-strand conformation polymorphism (SSCP) analysis of multiplex PCR products for detection of point mutations. Mutations detected by this screening method were characterized by DNA sequencing. DNA sequencing was performed using the ALFexpress DNA sequencer (Pharmacia Biotech).

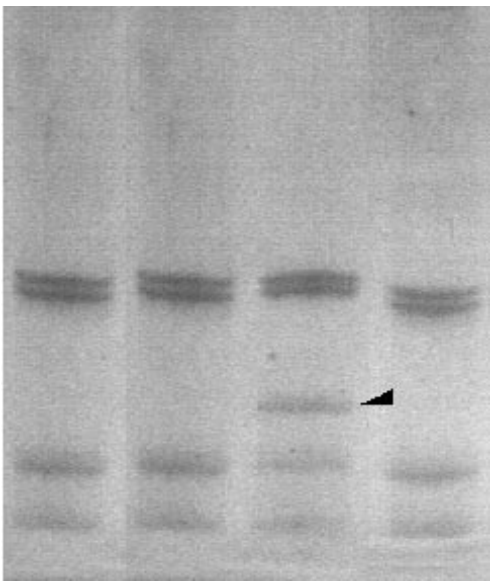
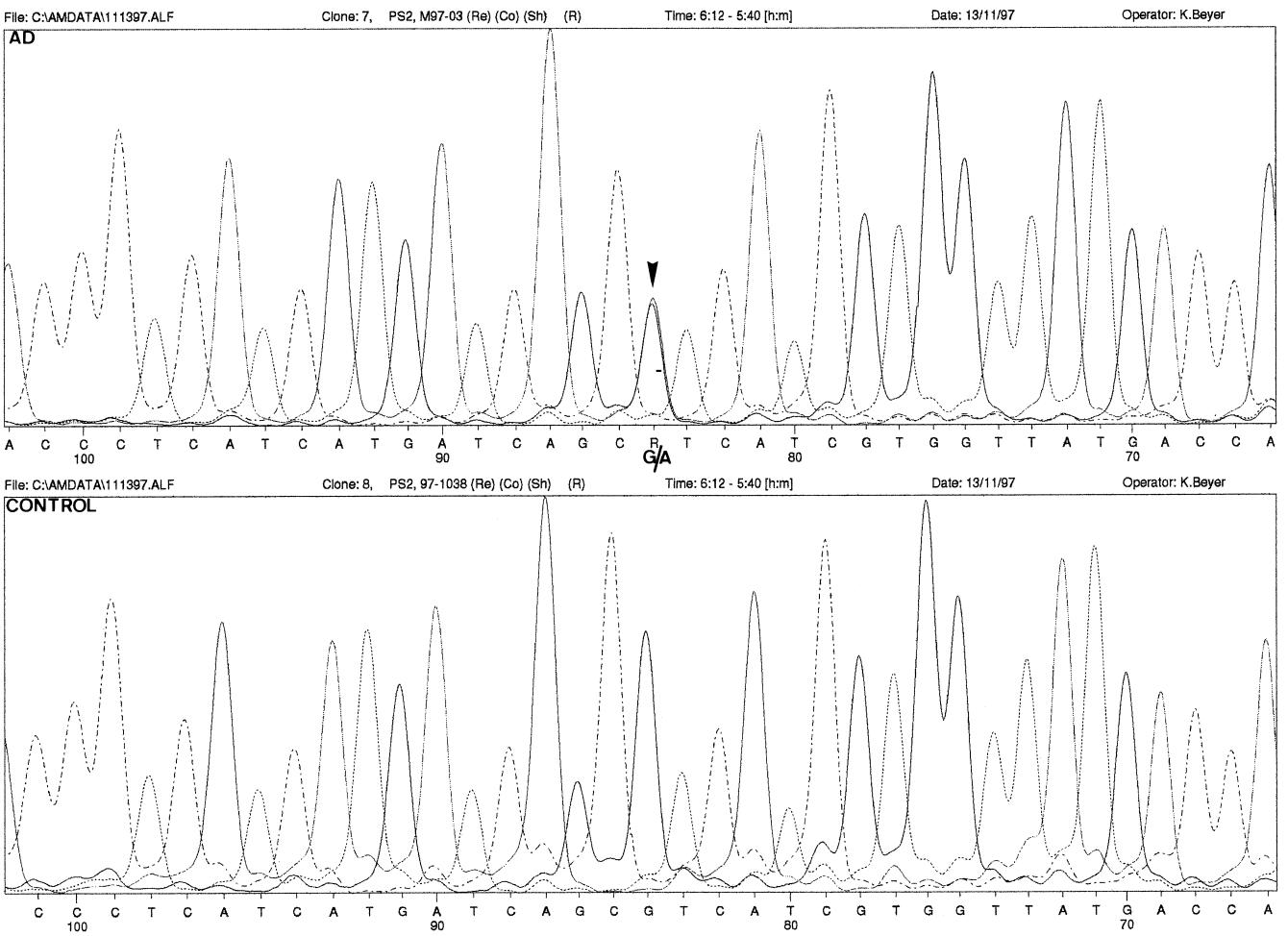


Fig. 1 Single-strand conformation polymorphism (SSCP) of TM2 polymerase chain reaction products. (➤ abnormal SSCP pattern)

Fig. 2 DNA sequence detected in the affected individual compared with a control sample (*AD* Alzheimer's disease)



RESULTS AND DISCUSSION

We detected an abnormal SSCP pattern affecting only 1 patient who had been clinically diagnosed as having late-onset AD [17] (Fig. 1). A missense mutation consisting of a G->A substitution on exon *5* of the *PS-2* gene (Fig. 2) was found by DNA sequencing which results in a Val to Ile substitution at codon 148 within the predicted TM2 domain of the *PS-2* protein. None of the other subjects of the present study carried the mutation. At the time of clinical diagnosis, aged 76 years, the patient was at the stage of moderately severe deficit (G3) according to the Global Deterioration Scale [19]. The age at disease onset was 71 years.

There were no known first-degree relatives known with dementia. However, he could not be considered as a sporadic case, because there were at least two other members of his family who had exhibited symptoms of probable dementia, but were not clinically diagnosed, and it is now impossible to recover further information.

In addition to *PS-2* screening, we carried out a similar genetic screening of *APP* and *PS-1* genes of this patient to exclude mutations. Since the patient presents an *APOE* genotype *ε3–ε3*, we excluded the influence of allele *ε4*, or the possible epistatic effect of the *ε2–ε3* genotype with the *PS-2* mutation, which might delay disease onset [20]. Therefore, it seems that the *V148I* mutation by itself has a pathogenic effect on the origin and clinical course of the AD exhibited by the carrier patient described.

The present report is consistent with the *N141I* mutation described by other authors within the predicted TM2 domain of the *PS-2* gene, since both mutations have been described in late-onset AD kindreds [12], whereas the mutation within the predicted TM5 domain was found in an EOAD pedigree [13]. Carriers of mutations within TM2 of *PS-1* have a mean age at onset of 40 years, while the other mutations in the *PS-1* gene occur in families with a mean age at onset of 47 years [14]. These data suggest that presenilins might have different roles in the etiopathogenesis of AD, since mutations within TM2 of *PS-2* seem to be associated with late-onset familial AD. In summary, the novel mutation we report here is the third mutation described in the *PS-2* gene and the first presenilin mutation detected in a Spanish AD patient.

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