# Alzheimer disease PS-1 exon 9 deletion defined

*To the editor*—The clinical, pathological, and genetic analyses of a Finnish pedigree (Finn2) with early-onset inherited Alzheimer disease (AD) have been reported[1]. This family demonstrated linkage to the PS1 region of chromosome 14, and analysis for PS1 mutations by RT–PCR and immunoblot demonstrated heterozygous deletion of exon 9, which has been shown to cause early-onset AD[2]. However, unlike a previously described family[2], no splice acceptor site mutation was detected in Finn2, suggesting the presence of either a small genomic deletion that included exon 9 or of mutations elsewhere that could affect splicing.

Intronic primers flanking exon 9 were designed using the PAC sequence available in the Genbank sequence database (clone DJ0054D12; accession number AC006342). PCR amplification of an approximate 6.5-kb region encompassing exon 9 showed the presence of an aberrant product that segregated with affected members of Finn2 (Fig. 1) and was not present in more than 150 alleles of a Finnish control population over 85 years of age. This band was later confirmed by sequencing to be the result of a 4,555-bp deletion (which we call the Δ9 Finn variant) between exons 8 and 10 and encompassing exon 9. To our knowledge, this is the first time a deletion has been shown to cause an autosomal dominant neurodegenerative disorder. Despite the gross nature of the mutation, like other pathogenic presenilin mutations, this does not disrupt the overall structure of the protein.

The clinical, pathological and etiological importance of Δ9 mutations has been discussed[1]. In addition to the presence of 'cotton wool' plaques and the scarcity of congophilic cored plaques typical of AD, there seems to be an association with the PS1Δ9 or PS1Δ9 Finn mutations and the occurrence of spastic paraparesis. However, because spastic paraparesis has only been described in two of four families with Δ9 variations and because it may also be associated with other PS1 missense mutations[3], the specific link between this symptom and Δ9 variations may be complex.

It will be useful to determine if other deletions exist in families in which Δ9 has been confirmed through RT–PCR or immunoblot experiments but in which splice-site mutations have not been found[3]. It is also important to check for this deletion in families in which early onset disease occurs but in which missense mutations have not been found, and in families whose members present with spastic paraparesis. If this precise deletion or similar deletions occur in other non-related families, it may indicate that a specific underlying mutation mechanism exists.

Finally, in addition to the obvious change at the protein level, we cannot exclude the possibility that the deletion seen in Δ9Finn also affects the transcriptional regulation, RNA stability or non-exon 9 splicing of PS1 in these families. Thus, there may be subtle phenotypic differences between Δ9Finn and Δ9 splice site mutations.

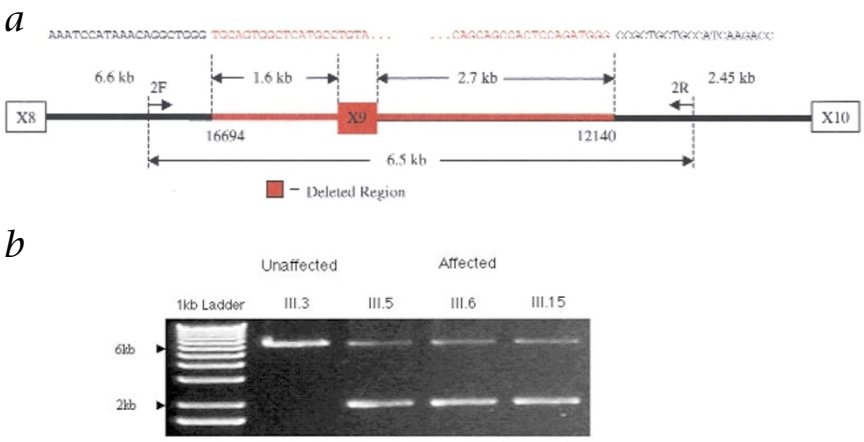


**Fig. 1** Genomic analysis of PS-1. PCR used intronic primers (2F, 5′–TTTAAATCTGCATATTTTCCAGCCAGGCATGAC–3′; 2R, 5′–AAAGCATTAGGTCTCATCCTTTAGTGCACG–3′) flanking exon 9, with the Expand Long PCR System. Cycling conditions were as described by the manufacturer (Hybaid Touchdown thermocycler, cycling conditions were as described by the manufacturer, except that a 'touchdown' program was used such that annealing temperatures gradually decreased from 62 °C to 55.1 °C over 30 cycles. The initial extension time was 4 min 15 s and was increased by 20 s/cycle beginning on the 11th cycle. Short PCR products (from affected individuals) and long PCR products derived from both affected and non-affected individuals in Finn2 were excised from low-melting-point agarose gel (FMC), purified using the QIAquick PCR Purification System (Qiagen), and sequenced on ABI377 (Perkin Elmer) using Big Dye chemistry. Primers used for sequencing (OAPS1R4, 5′–CTTTTCTATCAGGTTTACTAGTGGTCTTGATGGCAGC–3′; OAPS1F4, 5′–GATGTAAGGTGTTTGTGTTAAGGTGAAATGAAAAGTGA–3′) flanked deleted sequence. ***a***, Sequence proximal to exon 9 and the relative positions of primers 2F and 2R are shown. Nucleotide numbers at the deletion points are based on PAC sequence (accession number AC006342; clone number DJ0054D12). X8 and X10 are PS-1 exons 8 and 10 respectively. ***b***, PCR results showing the heterozygous deletion of the 4,555-bp region encompassing exon 9 in affected family members of Finn2. Lane 1, molecular size markers (sizes, left margin).

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