Screening of amyloid precursor protein gene mutation (APP 717 Val → Ile) in Swedish families with Alzheimer’s disease

Short Communication

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Summary. Screening for the APP 717 Val → Ile mutation in the amyloid precursor protein (APP) gene in 34 Swedish families with familial Alzheimer’s disease (FAD), 16 sporadic cases of Alzheimer’s disease and five patients with Down’s syndrome (DS) failed to identify further cases of the mutation. These results suggest that the mutation is rare among Swedish families with Alzheimer’s disease. In addition, we summarize present reports of the frequency of the mutation.

Keywords: Alzheimer’s disease, chromosome 21, amyloid precursor protein, genetics, Down’s syndrome.

Introduction

In 1991, a point mutation in the amyloid precursor protein gene, located on chromosome 21, was reported to segregate with affected members in two unrelated families with familial Alzheimer’s disease (Goate et al., 1991). Following this report three Japanese FAD families have been shown to carry the same mutation (Naruse et al., 1991; Yoshioka et al., 1991), one Canadian FAD family reported by Karlinsky et al. (1992), and one family identified by Fidani et al. (1992). The mutation is characterized as a missense mutation at codon 717 of the β-amyloid precursor protein gene in exon 17, leading to a shift of cytosine to a thymine. This led to a subtle change of valine to an isoleucine at the amino acid level of the transmembrane region (Goate et al., 1991).

Three additional mutations have been reported in the APP gene (Chartier-Harlin et al., 1991a; Murrell et al., 1991; Mullan et al., 1992a). Two of these mutations occur in the same codon (717) as the first report by Goate et al. (1991). One family has a thymine substituted with the second
guanine giving a phenyl-alanine instead of the valine (Murrell et al., 1991) and in the second mutation described by the London group, a thymine residue replaced the third guanine, in this case giving a glycine instead of the valine (Chartier-Harlin et al., 1991a). Mullan et al. (1992a) identified a double mutation in a Swedish family at codons 670 and 671 (APP 770 transcript) in exon 16, changing lysine to asparagine and methionine to leucine.

In total, four mutations have been detected in the APP gene so far. Together they support the hypothesis of being the pathogenic cause in these families. In contrast, AD is strongly suggested to be heterogenous. Linkage have been shown to both chromosome 19 (Pericak-Vance et al., 1991) and chromosome 14 (Mullan et al., 1992b; St George-Hyslop et al., 1992; Van Broeckhoven et al., 1992).

The effect of the APP mutations have been suggested to make the transmembrane region more hydrophobic and anchor the protein more firmly in the membrane, which could influence the stability of the deposited β-A4 peptide (Goate et al., 1991) or to alter translational regulation at the mRNA level of this protein. Translational regulation would allow both genetic and environmental factors to influence the APP production (Tanzi and Hyman, 1991). This may lead to increased levels of APP in individuals carrying the mutation. This increase would be similar to the situation in patients with Down's syndrome whom by definition carry a third copy of chromosome 21 and APP and an increased expression of APP (Tanzi et al., 1987; Rumble et al., 1989). In addition, they usually develop characteristic histopathological changes of Alzheimer's disease (Olson and Shaw, 1969).

Material and methods

We have screened for the APP717 Val → Ile mutation in 50 unrelated families with Alzheimer's disease (AD) assessed at our clinic, originating from Sweden and Norway (one family), five patients with Down's syndrome (DS) and 11 normal unrelated individuals. Thirtyfour families showed a familial aggregation of AD of which 22 families with an early onset (<65 years of age, range 50–65 years of age) and 12 families with late onset (range 66–83 years of age). Sixteen patients were sporadic cases of AD with an onset age ranging between 47–72 years of age. The cytological diagnosis in all patients with Down's syndrome are a complete trimsomi 21.

PCR amplification was carried out with DNA from lymphocytes in peripheral blood and used two primers (5′- cet cat cca aat gtc ccc gtc att-3′, 5′-gcc taa ttc tct cat agt ctt aat tcc cac-3′ (Goate et al., 1991) (KabiGen AB). The PCR-reaction started with annulling 94°C 2 min, followed by 30 cycles (denaturation 94°C, 1 min, annulling 37°C, 1 min, extension 72°C, 2 min) and finished by 72°C for 5 min. Taq I polymerase (Perkin-Elner) was used and the reaction solutions were according to the purchaser. The cycles were carried out in a thermal reactor (Hybaid). Bcl I (Boeringer Mannheim) was used to digest the PCR product over night, at 50°C under mineral oil (Sigma). Electro-phoresis was performed on 3% agarose (Pharmacia NA grade) gel stained with ethidium bromide in 1 X TBE buffer.

Results and discussion

None of the Swedish AD and DS patients and none of the 11 unrelated normal controls showed the Val → Ile mutation in exon 17 of the APP