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Review

Genetic susceptibility factors for Alzheimer's disease

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Abstract

Alzheimer's disease is the most frequent cause of dementia. Family and twin studies have suggested that genetic factors play a role in Alzheimer's disease development. Some Alzheimer's disease cases show an autosomal dominant inheritance pattern and thus allow the discovery of major disease genes. However, most Alzheimer's disease cases are sporadic. These cases are mainly due to the effects of several different genes and of interactions between genetic susceptibility factors and environmental factors. Such interactions are illustrated by the apolipoprotein E ε4 allele, associated with a higher risk of Alzheimer's disease. Other genetic susceptibility factors have been reported but variously confirmed in Alzheimer's disease: apolipoprotein E receptors, α2-macroglobulin or angiotensin I converting enzyme genes. Thus, except for a small percentage of Alzheimer's disease cases with a dominant inheritance pattern, the genetic component of the vast majority of cases is underlain by complex interactions of genetic susceptibility factors and environmental conditions.

Keywords: Alzheimer's disease; Gene environment interaction; Genetic susceptibility factor; Apolipoprotein E

1. Introduction

In occidental countries with an ageing population, the incidence and prevalence of dementia and its common subtype, Alzheimer's Disease rise exponentially with increasing age (Hofman et al., 1991; Rocca et al., 1998). Alzheimer's disease is a progressive neurodegenerative disorder, which causes memory loss and alters higher intellectual functions. Usually, death occurs 8 to 10 years after the date of the clinical onset.

No biological markers or specific clinical features exist that would allow a definite diagnosis of Alzheimer's disease. A definite diagnosis requires the demonstration of neuropathological lesions in the brain. The essential histopathological features of Alzheimer's disease are characterised by a selective neuronal loss associated with neurofibrillary tangles in the neurons and deposition of amyloid substance in senile plaques and cerebral blood vessels. Neurofibrillary tangles consist primarily of microtubule-associated tau proteins. The normal function of tau proteins is to stabilise microtubules of the neuronal cytoskeleton. This function is regulated by phosphorylation and dephosphorylation processes. Microtubule-associated tau proteins become abnormally hyperphosphorylated and accumulate as paired helical filament tangles in neurons undergoing degeneration. Senile plaques are mainly built up by the deposition of β-amyloid protein in brain parenchyma. β-amyloid is a proteolytic fragment of a larger precursor, the β-amyloid precursor protein (APP). Plaques and tangles exist in normal aging brain but are considerably less numerous and less widely distributed than in Alzheimer's disease.

In general, there is a great variability of age at onset for Alzheimer's disease patients. The age at onset of the disease allows classification of Alzheimer's disease as early-(before 65 years) and late-(after 65 years) onset. In more than 90% of cases, Alzheimer's disease develops after 65 years of age. Several environmental risk factors have been associated with an increased risk of Alzheimer's disease, such as head injury with loss of consciousness, while other factors have been associated with a decreased risk, such as high educational levels (Table 1).

A family history of dementia is a risk factor for Alzheimer's disease. Twin studies have shown better concordance for monozytic than for dizygotic twins suggesting the existence of a genetic component in Alzheimer's disease (Raiha et al., 1996). Some Alzheimer's disease cases, mainly early-onset ones, show an autosomal domi-

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Table 1
Potential risk factors of Alzheimer's disease

Risk factors
Age
Family history of dementia
Head injury
Down syndrome
Parkinson's disease
Depression
Hypothyroidism
Increased aluminium concentration in drinking water
Tobacco consumption
Alcohol abuse
Vascular risk factors
Early and late parental age
Protective factors
High educational level
Moderate wine consumption
Use of hormone replacement therapy for women
Use of anti-inflammatory drugs

nant inheritance pattern due to the presence of a major gene effect (Table 2). Most Alzheimer's disease cases are sporadic, that is with no evidence of Mendelian transmission. However, sporadic cases often have a positive family history of dementia (Frisoni and Trabucchi, 1997). This suggests that the members of these families may share common environment and/or genetic factors. Although differentiation between these genetic and environmental determinants is difficult because of complex interactions, most late-onset cases are probably due to the effect of several different genes, their penetrance being influenced by age and other environmental and/or genetic factors (Table 2). Under these conditions, the impact of a gene in such a multifactorial design may correspond to a genetic susceptibility risk factor, predisposing, under certain conditions, to the development of a neurodegenerative disease.

2. Autosomal dominant mutations

Until now, for autosomal dominant cases of Alzheimer's disease, mutations have been discovered in three different genes. The first genetic locus associated with early-onset familial Alzheimer's disease was found on the APP gene located on chromosome 21 in 1991 (Goate et al., 1991). Several missense mutations were detected within the APP gene in various families (Chartier-Harlin et al., 1991; Sorbi et al., 1995b). APP isoforms are integral membrane glycoproteins that have a large ectodomain, an amyloid region and a short cytoplasmic tail. The functions of APP are still unknown.

Genetic linkage studies showed that a gene associated with autosomal dominant forms of Alzheimer's disease was located on chromosome 14 (Schellenberg et al., 1992). Positional screening of the chromosomal region identified on chromosome 14 subsequently allowed isolation of a new gene, the presenilin 1 gene (*PS-1*) (Sherrington et al., 1995). *PS-1* encodes a 467 amino-acid protein, an integral membrane protein with eight transmembrane domains. Another gene linked with familial Alzheimer's disease has been identified on human chromosome 1, based on its high degree of similarity with PS-1, the presenilin 2 gene (*PS-2*) (Levy-Lahad et al., 1995a, b). The first *PS-2* mutation was described in a group of families descending from a single German family (Levy-Lahad et al., 1995a). Another mutation was in an Italian family (Rogaev et al., 1995). PS-1 and PS-2 functions are unknown. Some evidence suggests that PS-1 and -2 could be implicated in both neuronal differentiation during neurogenesis (Capell et al., 1997) and neurite outgrowth (Dowjat et al., 1999).

Mutations of *APP*, *PS-1* and *PS-2* are responsible for various proportions of all cases of autosomal dominant Alzheimer's disease. *APP* mutations account for 2% to 3%, *PS-1* mutations for about 50% to 80% of these cases and *PS-2* mutations are very rare (Fig. 1). However, these autosomal dominant forms of Alzheimer's disease represent only 5% of all Alzheimer's disease cases. Most Alzheimer's disease patients have the sporadic form of the disease but for these Alzheimer's disease cases, genetic susceptibility factors could also increase or decrease the risk of developing the disease.

3. Genetic susceptibility risk factors and Alzheimer's disease

In the last few years, several genetic susceptibility factors of Alzheimer's disease have been proposed. The

Table 2
Differences between genetic disease and genetic susceptibility

	Genetic disease	Genetic susceptibility
Age at onset	Early onset	Late Onset
Genetic component of disease	Mutation associated with the disease	Mutation associated with an increased risk
Mutation frequency	Rare	Frequent
Inheritance	Mendelian pattern	Complex pattern
Individual effect	Major	Weak
Population effect	Weak	Major
Interaction with environmental factors	Weak interaction	Major

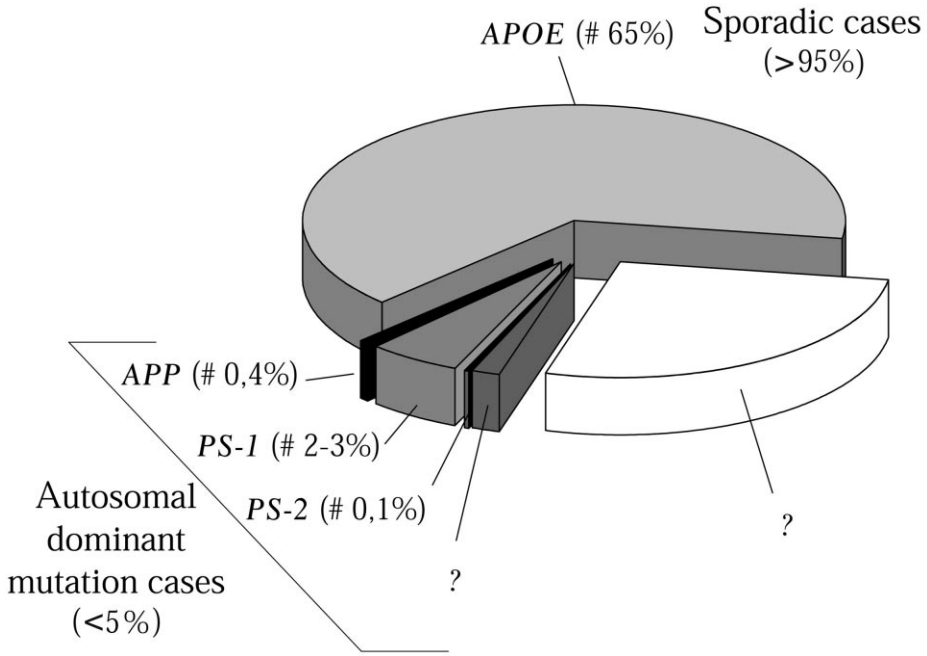

Fig. 1. Distribution of Alzheimer's disease forms and of their related genetic susceptibility factors.

best-documented one so far is the apolipoprotein E gene polymorphism.

3.1. Apolipoprotein E

Apolipoprotein E is a 299 amino-acid protein implicated in the regulation of cholesterol and triglyceride metabolism. Apolipoprotein E is coded by a gene (*APOE*) located on chromosome 19 (Fig. 2), and exists as three frequent alleles *ε2*, *ε3*, and *ε4*. Subjects with the *ε4* allele have higher levels of total and low density lipoprotein (LDL) cholesterol compared with *APOE ε3/ε3* bearers (Dallongeville et al., 1992). The *ε4* allele bearer subjects have higher risks of coronary heart disease than do subjects without this allele (Eichner et al., 1993).

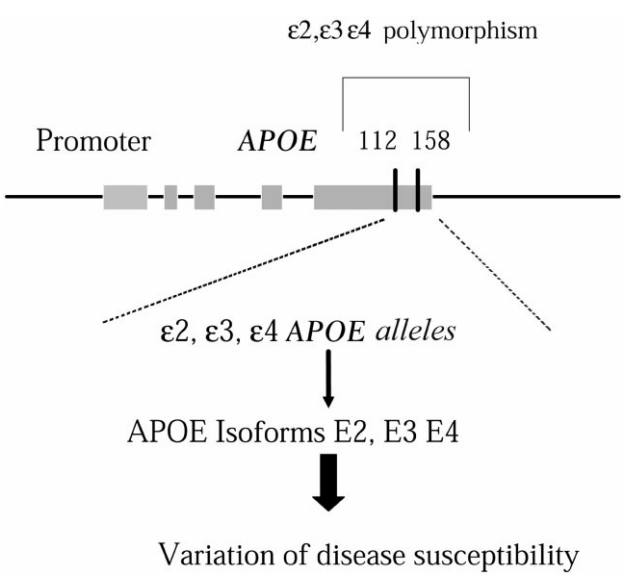

Fig. 2. The apolipoprotein E gene.

3.1.1. APOE and Alzheimer's disease

Apolipoprotein E is synthesised in the central nervous system and plays a major role in normal brain lipid metabolism. Immunohistochemistry has allowed detection of apolipoprotein E in senile plaques in the brain of Alzheimer's disease patients (Namba et al., 1991). In 1993, Strittmatter et al., found that *APOE ε4* allele was associated with an increased risk of Alzheimer's disease development in a familial late-onset Alzheimer's disease population (Strittmatter et al., 1993). Since 1993, this result has been confirmed in almost all studies dealing with late- and early-onset Alzheimer's disease (Brousseau et al., 1994; Farrer et al., 1997; Schmechel et al., 1993). In a meta-analysis published by Farrer et al. (1997), the risk associated with *APOE ε4* allele in a Caucasian population was 12.5 for homozygous subjects and 2.7 for heterozygous subjects, suggesting a gene dose effect. Longitudinal studies confirmed the impact of *APOE ε4* allele on Alzheimer's disease (Havlik et al., 2000; Slooter et al., 1998). Moreover, the presence of *APOE ε4* allele may also be associated with an age-related cognitive decline (Berr et al., 1996). Conversely, a protective effect of the *APOE ε2* allele on Alzheimer's disease and age-related cognitive decline was reported (Chartier-Harlin et al., 1994; Farrer et al., 1997). The mean age at onset of the disease decreases as the number of *APOE ε4* alleles increases (Chartier-Harlin et al., 1994). The *APOE ε4*-associated risk of Alzheimer's disease varies widely with age. This

risk increases after 40 years (up 60–75 years) but declines in the oldest age groups (Farrer et al., 1997).

3.1.2. APOE and pharmacogenetics

Symptomatic treatments have been developed in attempts to slow down Alzheimer's disease progression. Pharmacological treatments of Alzheimer's disease were targeted to increase cholinergic activity in the central nervous system of Alzheimer's disease patients who have a marked loss of presynaptic cholinergic neurons. The most widely used drugs are cholinesterase inhibitors that prevent the degradation of released acetylcholine. Several cholinesterase inhibitors have been tested. Their efficacy for symptomatic treatment has been proven but shows large individual variations.

APOE ε4 allele patients seem to have a more severe cholinergic deficit than do non-*APOE ε4* allele bearers (Poirier et al., 1995). Thus, *APOE ε4* Alzheimer's disease bearers may have a different level of response to acetylcholinesterase inhibitor therapies. This hypothesis has been tested with tacrine. The effects of *APOE* genotype on the clinical response of Alzheimer's disease patients to 30 weeks of tacrine treatment were evaluated retrospectively (Poirier et al., 1995). A higher frequency of responders was observed in non-*ε4* bearers. However, in this latter study, no placebo group was analysed and some authors have emphasised that the effect observed was not due to tacrine itself but to the natural course of the disease according to *APOE ε4* allele status. Another study, using a placebo group control, slightly confirmed these results, but only in women (Farlow et al., 1998). Three other cholinesterase inhibitors, donepezil, metrifonate and galantamine, tested in Alzheimer's disease symptomatic treatment were analysed in relation to *APOE ε4* allele status. No effect dependent on the *APOE* genotype could be shown (Farlow et al., 1999; Greenberg et al., 2000; Raskind et al., 2000; Tariot et al., 2000). Drugs acting on neurotransmitter pathways other than that of acetylcholine have also been tested for the symptomatic treatment of Alzheimer's disease. For instance, S12024 facilitates the activity of brain noradrenergic and vasopressinergic systems altered in Alzheimer's disease brains. S12024 significantly reduced the decrease of the Mini Mental State Examination score compared to the effect of placebo in *APOE ε4* allele bearers, whereas no effect could be detected for *APOE ε4* allele non-bearers (Richard et al., 1997) (Fig. 3).

These pharmacogenetic approaches involving *APOE* polymorphism have also been extended to various Alzheimer's disease clinical trials involving drugs as anti-inflammatory products or hormone replacement therapy in women.

3.1.3. APOE, biological hypotheses

The mechanisms by which *APOE* polymorphism is implicated in Alzheimer's disease are not fully understood. Several hypotheses have been proposed to explain this association. Firstly, the E4 isoform would facilitate or at least not limit amyloid substance deposition. Neuropathologic studies reported that, indeed, patients bearing one *APOE ε4* allele had an increased density of senile plaques and β-amyloid deposition (Berr et al., 1994). Apolipoprotein E4 isoform binds β-amyloid peptide with a higher affinity than does apolipoprotein E3 (Strittmatter et al., 1993). *APOE ε4* allele has also been related inconsistently to the development of neurofibrillary tangles, with some studies showing a positive correlation (Ohm et al., 1995) and others not (Gomez-Isla et al., 1996). In vitro, biochemical isoform-dependent interactions between apolipoprotein and tau protein have been described: apolipo-

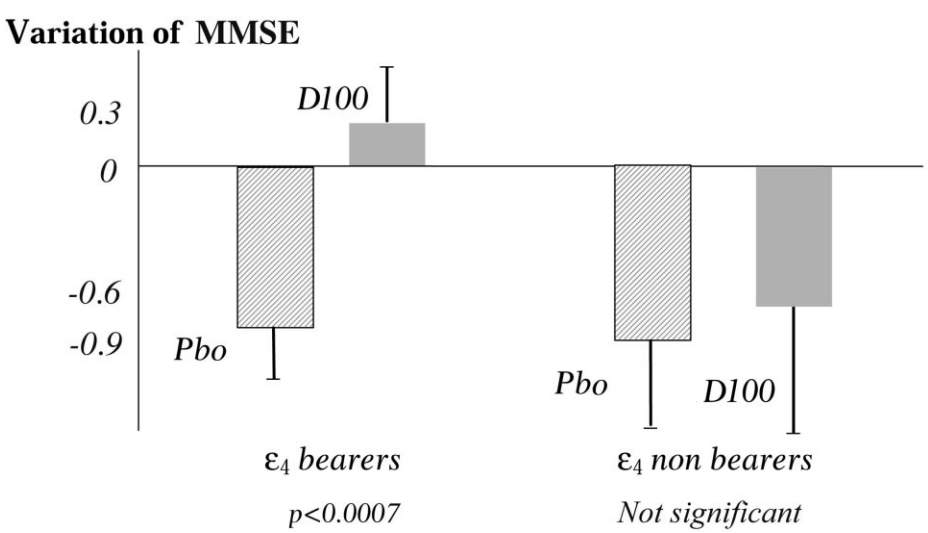

Fig. 3. APOE genotypes and pharmacogenetics of Alzheimer's disease. Variation of the Mini-Mental State Examination (MMSE): (mean and standard error) after 12 weeks of exposure to 100 mg of S12024 (D100) or placebo (Pbo) stratified on the presence or absence of ε4 allele in the genotype of the patients.

protein E3 isoform has an affinity for tau protein higher than does apolipoprotein E4 isoform (Strittmatter et al., 1994). Oxidative stress could also be implicated in the occurrence of Alzheimer's disease. Apolipoprotein E4 isoform may not protect against oxidative stress in contrast to E2 isoform (Miyata and Smith, 1996). Another possible explanation is that apolipoprotein E could be involved in the pathogenesis of Alzheimer's disease through its effects on dyslipidemia, atherosclerosis and vascular diseases. The presence of cerebrovascular disease is associated with more severe forms of Alzheimer's disease (Snowdon et al., 1997). An interaction between *APOE* and atherosclerosis has been reported: subjects with at least one *APOE ε4* allele and atherosclerosis symptoms had the highest risk of Alzheimer's disease while subjects without *APOE ε4* allele and without atherosclerosis had the lowest risk. Subjects with one or two *ε4* alleles but without atherosclerosis, or subjects with atherosclerosis and with *ε3/ε3* genotype had intermediate levels of risk (Hofman et al., 1997). Apolipoprotein E may be considered as a protein implicated in nerve repair and growth in the peripheral and central nervous system. In various cell lines, apolipoprotein E3 isoform seems to increase growth and branching of neurites, whereas apolipoprotein E4 has an opposite effect (Bellosta et al., 1995; Nathan et al., 1994). *APOE ε4* allele has been associated with a worse prognosis for post-brain traumatic injury (Sorbi et al., 1995a); moreover, an increased frequency of the *APOE ε4* allele has been shown in other types of dementia, such as Lewy body disease (St. Clair et al., 1994) or Creutzfeldt–Jacob disease (Amouyel et al., 1994). Another possible way to explain *APOE ε4* impact on Alzheimer's disease relies on the inflammatory hypothesis. Alzheimer's disease patients have neuropathological signs of inflammation as suggested by microglia activation, increased expression of acute phase proteins, cytokines and complement factor. Apolipoprotein E could inhibit microglia activation induced by β-amyloid (Laskowitz et al., 1998).

Thus, apolipoprotein E has been, and is being extensively studied. It is a very important susceptibility factor for Alzheimer's disease development, but its presence is neither necessary nor sufficient, suggesting the implication of other risk factors and possibly other susceptibility genes.

3.2. APOE expression and the APOE promoter

Other genetic variants influencing *APOE* allele expression may account for increased or decreased levels of Alzheimer's disease risk. The *APOE* locus itself may modulate this risk. Preliminary observations described an overexpression of the *APOE ε4* allele when compared with the *APOE ε3* allele in the brain of patients with Alzheimer's disease but not in *ε3ε4* controls (Lambert et al., 1997). Variations in the promoter region regulating *APOE* gene expression could explain these observations. Detailed genetic analysis around the *APOE* locus has suggested the existence of genetic variability in the *APOE* promoter (Chartier-Harlin et al., 1994). Three polymorphisms in the promoter of *APOE* have been analysed in relation with Alzheimer's disease risk.

Case-control studies suggested that the A allele of an A/T polymorphism in the *APOE* regulatory region at position −491 was associated with increased risk of Alzheimer's disease (Bullido et al., 1998; Lambert et al., 1998a). However, other studies did not support this observation (Chen et al., 1999; Song et al., 1998; Thome et al., 1999). Another polymorphism was located in the *APOE* promoter region, at position −427; the −427 C allele has been reported in one study as a potential risk factor for Alzheimer's disease (Artiga et al., 1998) but in another study, it was the T allele frequency that was increased in Alzheimer's disease (Zurutuza et al., 2000). A G → T polymorphism at position −219 on *APOE* promoter has also been described, and the −219 T allele has been associated with increased Alzheimer's disease risk (Lambert et al., 1998c).

3.3. Apolipoprotein E receptors

Apolipoprotein E receptors constitute interesting candidate genes able to interact with apolipoprotein E. In the brain, the apolipoprotein E-containing lipoproteins secreted by astrocytes are transported into other brain cells via receptor-mediated endocytosis. Several apolipoprotein E receptors belonging to the LDL receptor superfamily are present in the brain. Two of these receptors have been particularly studied in relation with Alzheimer's disease, the LDL receptor-related protein (LRP) and the Very Low Density Lipoprotein receptor (VLDL-receptor).

3.3.1. LRP

The LRP is the main apolipoprotein E receptor in the brain. LRP interacts with many ligands such as apolipoprotein E, APP, α2-macroglobulin and is present in senile plaques (Rebeck et al., 1993). In vitro studies have shown that the apolipoprotein E isoform neurite outgrowth is mediated by the LRP (Fagan et al., 1996). Kounnas et al. (1995) have shown that LRP mediates the endocytosis and degradation of the APP also.

The LRP gene has a tetranucleotide repeat $(TTTC)_n$ polymorphism that generates four different alleles: two frequent alleles of 91 and 87 base pairs (bp) and two rare alleles of 95 and 83 bp. An association between the 87 bp allele and increased risk for late-onset Alzheimer's disease has been reported for a Caucasian population (Lendon et al., 1997); in two European populations, opposite results were found with enrichment of the *LRP* 91 allele in Alzheimer's disease patients compared to the control group (Lambert et al., 1999; Wavrant-DeVrieze et al., 1997). However, most of the studies published so far could find no association between this polymorphism and Alzheimer's disease (Clatworthy et al., 1997; Fallin et al., 1997; Scott

et al., 1998). Another polymorphism has been described in association with Alzheimer's disease, a common C766T polymorphism located in exon 3. Association of the C allele with higher Alzheimer's disease risk has been found in several studies (Kamboh et al., 1998; Kang et al., 1997; Lambert et al., 1998b), while others failed to replicate these results (Beffert et al., 1999; Kamboh et al., 1998; Woodward et al., 1998). In 1999, Beffert et al., in a meta-analysis, pooled the data from seven studies, and found that C allele frequency was significantly increased in Alzheimer's disease compared to that in the controls but that the association level was weak (Beffert et al., 1999).

Since the two previous *LRP* polymorphisms do not seem to affect protein function, they may be in linkage disequilibrium with another Alzheimer's disease disease locus nearby on chromosome 12, often suspected in genome scans (Pericak-Vance et al., 1997; Rogaeva et al., 1998), like the transcriptional factor gene, *LBP-1*, recently described as a potential risk factor for Alzheimer's disease (Lambert et al., 2000).

3.3.2. VLDL-receptor

The VLDL-receptor is closely related structurally and functionally to the LRP. The VLDL-receptor plays a major role in peripheral lipid trafficking. VLDL-receptor binds numerous ligands, such as apolipoprotein E and α2-macroglobulin. The VLDL-receptor is expressed in normal brain and in senile plaques of Alzheimer's disease patients (Okuizumi et al., 1995).

The *VLDL-receptor* gene, on chromosome 9, contains a trinucleotide repeat $(CGG)_n$ polymorphism in the 5′ untranslated region, with eight alleles, from 4 to 11 repeats. The results of case-control studies designed to evaluate the effect of *VLDL-receptor* polymorphism as risk factor for Alzheimer's disease are inconsistent. The *VLDL-receptor* 5-repeat allele was associated with Alzheimer's disease cases aged less than 75 years in a Japanese population, independently of *APOE* polymorphism status (Okuizumi et al., 1995). Another study in Japanese population partly confirmed these results for early-onset Alzheimer's disease (Yamanaka et al., 1998). Conversely, in two studies with Asian populations, the *VLDL-receptor* polymorphism was not a risk factor for Alzheimer's disease (Arinami et al., 1996; Chen et al., 1998). Caucasian populations also yield controversial results. In early-onset Caucasian subjects, the absence of the *VLDL-receptor* 8-repeat allele was associated with an increased risk of Alzheimer's disease (Brookes et al., 1997) while other reports were not able to detect any association (Lendon et al., 1997; Pritchard et al., 1996). In a European population, the *VLDL-receptor* 5-repeat allele frequency was significantly increased only in patients bearing at least one *APOE ε4* allele (Helbecque et al., 1998), mainly in late-onset forms. In a Northern Ireland population, McIlroy et al. (1999) reported that the *VLDL-receptor* 9/9 genotype was a risk factor for Alzheimer's disease. These inconsistencies may be attributed to differences in allele frequencies in Asian and Caucasian populations. Indeed, the *VLDL-receptor* 8-repeat allele is absent in Asian populations, whereas the most frequent ones in Caucasian population are the 5-, 8-, and 9-repeat alleles.

3.4. α2-macroglobulin

Linkage analyses have provided evidence for a locus on the short arm of chromosome 12 and in late-onset familial Alzheimer's disease (Pericak-Vance et al., 1997; Rogaeva et al., 1998). α2-macroglobulin gene codes a pan-protease inhibitor, and is located in the chromosome 12 candidate region. α2-macroglobulin antibodies immunostain senile plaques (Rebeck et al., 1995), and α2-macroglobulin binds β-amyloid with a high affinity (Du et al., 1997). α2-macroglobulin has been implicated biochemically in the degradation and the clearance of β-amyloid via endocytosis through LRP (Narita et al., 1997). Thus, α2-macroglobulin could be considered as a possible candidate gene.

At least six polymorphisms have been described in the α2-macroglobulin gene locus. Two of them have been studied extensively in relation to Alzheimer's disease. One polymorphism is responsible for a 5 bp deletion in exon 18 and is characterised by two alleles: a wild-type allele and a deletion allele. Using the sibship disequilibrium test, a family-based association test, Blacker et al. (1998) reported an association between this deletion allele and Alzheimer's disease. The same was suspected in another family based-study with a borderline association (Rudrasingham et al., 1999), but was not seen in all studies (Rogaeva et al., 1999). In some case-control studies with unrelated subjects, an association between Alzheimer's disease and the deletion allele has been reported but the association was lower that that described by Blacker et al. (Dodel et al., 2000) and concerned only a subgroup of very old patients (Alvarez et al., 1999b). However, most case-control studies could not replicate this association (Chen et al., 1999; Crawford et al., 1999; Hu et al., 1999b; Rogaeva et al., 1999; Rudrasingham et al., 1999; Singleton et al., 1999). The second polymorphism is a valine (GTC)-to-isoleucine (ATC) change at codon 1000. Liao et al. (1998) reported an increased frequency of the G/G genotype in Alzheimer's disease compared to the controls but this result could not be replicated in other studies (Crawford et al., 1999; Singleton et al., 1999; Wavrant-DeVrieze et al., 1999). All these results tend to suggest that although the possibility is attractive, α2-macroglobulin is not or is only very weakly involved in Alzheimer's disease.

3.5. Angiotensin I converting enzyme

In agreement with the vascular hypotheses suggested for Alzheimer's disease, the renin angiotensin system has been implicated as a potential source of candidate genes. The renin angiotensin system is implicated in the regulation of arterial blood pressure. Two key enzymes are

involved (Fig. 4), renin and angiotensin I converting enzyme. The angiotensin I converting enzyme gene (*ACE*) is located on chromosome 17 and codes a 1306 amino-acid protein. An insertion/deletion polymorphism has been described in the *ACE* gene. This polymorphism is characterised by the presence (insertion: I) or absence (deletion: D) of a repetitive sequence of 287 bp in intron 16. The insertion/deletion polymorphism explains 40 to 50% of the interindividual variation in angiotensin I converting enzyme concentrations (Rigat et al., 1990). The DD subjects have the highest angiotensin I converting enzyme concentrations, II subjects, the lowest, and ID subjects have intermediate levels. D allele bearers have been inconsistently reported to have an increased risk of myocardial infarction, of restenosis after angioplasty, of left ventricular hypertrophy, of dilated cardiomyopathy (Amant et al., 1997; Cambien et al., 1994; Harn et al., 1995; Perticone et al., 1997).

The renin angiotensin system components are detected in the central nervous system (Bunnemann et al., 1993). Alzheimer's disease patients have increased densities of angiotensin I converting enzyme in some brain region and decreased angiotensin I converting enzyme activities in cerebrospinal fluid (Arregui et al., 1982; Zubenko et al., 1985). In vitro studies have shown that angiotensin II decreased acetylcholine release (Barnes et al., 1990). In animals, increased levels of angiotensin II could influence the cognitive processing acquisition and recall of newly learned tasks (Baranowska et al., 1983).

The *ACE D* allele has been associated with age-related memory impairment (Amouyel et al., 1996; Palumbo et al., 1999; Richard et al., 2000). However, the reports of association between *ACE* polymorphism and Alzheimer's disease lead to inconsistent results. Some studies have shown an association between the *ACE I* allele and a higher risk of Alzheimer's disease (Alvarez et al., 1999a; Hu et al., 1999a; Kehoe et al., 1999). Two other studies failed to show any association between *ACE* polymorphism and Alzheimer's disease (Chapman et al., 1998; Scacchi et al., 1998). Farrer et al. (2000) have found an association between the D allele and a higher risk of Alzheimer's disease only in a subgroup of subjects aged between 66 and 70 years. Crawford et al. (2000) reported that ID genotype bearers had a higher Alzheimer's disease risk compared to II or DD bearers whereas Narain et al. (2000) found the reverse: I or D homozygous subjects have increased Alzheimer's disease risk compared to ID genotype bearers. These conflicting results may be due to variability in the genetic background of the population studied, to sampling biases or to complex interactions with the other candidate genes of the renin angiotensin system.

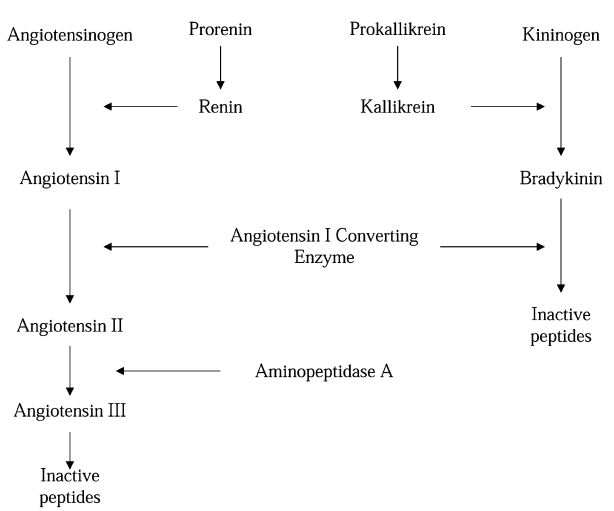

Fig. 4. The renin angiotensin system.

3.6. Other genetic susceptibility factors

Other genetic susceptibility factors have been reported in association with sporadic Alzheimer's disease: α1-antichmotrypsin gene that has been located in senile plaques, *PS-1*, *PS-2*, genes encoding for inflammatory proteins, FE65 protein, methylenetetrahydrofolate reductase, nitric oxide synthase, paraoxonase, cathepsin D, serotonine transporter, mitochondrial genes, butyrylcholinesterase, myeloperoxidase, dipeptidyl carboxypeptidase 1. Most of these factors still await confirmation, while others such as α1-antichymotrypsin (Haines et al., 1996; Helbecque et al., 1996; Muller et al., 1996; Tang et al., 2000) and butyrylcholinesterase (Brindle et al., 1998; Crawford et al., 1998; Kehoe et al., 1998; Singleton et al., 1998) have been definitely excluded.

4. Conclusion

As for most chronic diseases, a long-term complex multifactorial process may be at the origin of Alzheimer's disease. Multiple environmental and genetic determinants interacting all through life may create susceptibility to Alzheimer's disease.

Other than those regarding *APOE* genetic susceptibility findings are not consistent and often lack independent confirmation. Several possible explanations have been advanced to explain these discrepancies: regional population differences in Alzheimer's disease susceptibility associated with the polymorphism, interaction with age and longevity, linkage disequilibrium with another functional variant closely linked to a gene conferring Alzheimer's disease risk.

Among the different ways used to understand a disease, genetics has now clearly demonstrated its ability to help unravel new clues. Recently boosted by the Human Genome Project and the dramatic development of high throughput technologies, the neurological sciences have taken over genomic concepts to hunt for new genetic

susceptibility factors of Alzheimer's disease. These highly integrated genomic strategies are the most appropriate to tackle the multifactorial nature of such complex diseases. There are as many genetic potential determinants of Alzheimer's disease as there are proteins involved in the multiple pathways leading to neurodegenerative diseases. The recent development of biotechnology combining computer sciences and molecular biology helps with collecting large amounts of data that may help to offer a new paradigm of the molecular complexity of these diseases. These approaches to neurological diseases, by their molecular causes, rather than through their symptoms, will be rapidly integrated to boost pharmacogenomic and pharmacogenetic programs. Firstly, this will allow to discover new leads intended to cure disease rather than symptoms. Secondly, individual susceptibility will be introduced into clinical trials to test if a new (or an already marketed) susceptibility compound should be prescribed preferentially in a subgroup of population. However, this attractive molecular approach will still have to find its way among the numerous leads already in the pharmaceutical development pipeline. Large samples of patients, new strategies and a heavy workload will be needed to transform genomic concepts into disease management reality.

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