REVIEW

RISK AND PROTECTIVE FACTORS FOR SPORADIC ALZHEIMER'S DISEASE

Z. STOŽICKÁ, N. ŽILKA, M. NOVÁK*

Institute of Neuroimmunology, Slovak Academy of Sciences, Dúbravská cesta 9, 845 10 Bratislava, Slovak Republic

Received Septenber 3, 2007; accepted November 16, 2007

Summary. – Alzheimer's disease (AD) is the most common form of senile dementia. There are 24.3 million people suffering from this progressive neurodegenerative disorder worldwide. A century ago, AD was characterized with regard to the clinical manifestations and pathology for the first time. Up till now, there is a lack of full understanding of the underlying causes and molecular mechanisms leading to this progressive form of dementia. The majority of AD cases occur sporadically, what suggested that they could arise through interactions among various genetic and environmental factors. Current epidemiological investigations show that midlife hypertension, cardiovascular diseases, hypercholesterolemia, diabetes, obesity, inflammation, and viral infections can significantly contribute to the development and progression of AD, whereas active engagement in social, mental and physical activities may delay the onset of the disease. Apolipoprotein E (ApoE) is considered as the main genetic risk factor in the sporadic AD that is closely connected to lipid metabolism. Other genes involved in the disease pathways related to AD pathology in addition to cholesterol metabolism, neuroinflammation, amyloid and tau cascade, neuronal signalling, and plasticity are under investigation. In spite of the significant progress achieved, it is still not clear how genetic vulnerability and environmental exposures may contribute to the susceptibility of the disease. Therefore, understanding the role of disease-related risk factors for AD pathogenesis may help to identify specific modifiable risk factors that could provide possibility for the prevention of Alzheimer's dementia.

Key words: Alzheimer's disease; risk factors; hypertension; inflammation; apolipoprotein E

*Corresponding author. E-mail: michal.novak@savba.sk; fax: +4212-54774276.

Abbreviations: Aß = amyloid beta; ABCA1 = ATP-binding cassette transporter 1; ACE = angiotensin I converting enzyme; ACT = alpha-1-antichymotrypsin; AD = Alzheimer's disease; APOC1 = apolipoprotein C1, APOE = apolipoprotein E gene; ApoE = apolipoprotein E; APP = amyloid precursor protein; BDNF = brain-derived neurotrophic factor; CH25H = cholesterol 25-hydroxylase; CHRNB2 = nicotinic acetylcholine receptor, beta 2 subunit; CSF = cerebrospinal fluid; CST3 = cystatin C; CYP46A1 = cholesteol 24-hydroxylase; DNMBP = dynamin-binding protein; ESR1 = estrogen recdeptor alpha; HLA = human leukocyte antigen; IDE = insulin degrading enzyme; IL-1A = interleukin 1A gene; IL-1α = interleukin 1 alpha, IL-1ß = interleukin 1 beta; IL-6 = interleukin 6; IL-10 = interleukin 10; LH = luteinizing hormone; LPL = lipoprotein lipase; MAPT = microtubule-associated protein tau; MHC = major histocompatibility complex; NCSTN = nicastrin; NFT(s) = neurofibrillary tangle(s); PRNP = prion protein; PUFA = polyunsaturated fatty acid; SORL1 = sortilin related receptor; TFAM = transcription factor A, mitochondrial; TGFß = transforming growth factor beta; tHcy = total plasma homocysteine; TNFα = tumor necrosis factor alpha; UBQLN1 = ubiquilin

Contents:

1. Introduction

AD is a multifactorial neurodegenerative disorder with unknown primary cause. It becomes one of the greatest medical, social and economical problems, especially in the developed countries with steadily growing life expectancy. Epidemiologic studies show that currently 24.3 million people are suffering from dementia with 4.6 million new cases emerging each year (Ferri *et al.*, 2005). This disease is puzzling by its complexity involving multiple pathogenetic factors, intrinsically disordered proteins, truncated and hyperphosphorylated tau protein and ß-amyloid (cleavage product of amyloid precursor protein) (Grundke-Iqbal *et al.*, 1986; Wischik *et al.*, 1988; Novák *et al.*, 1991, 1993; Hardy and Selkoe, 2002; Masters and Beyreuther, 2006). Accumulation of misfolded proteins initiates pathogenic pathways leading to neurodegeneration, inflammation, glutamate excitotoxicity, cholinergic deficit, imbalance of neurotransmitters, mitochondrial dysfunction, oxidative stress, calcium homeostasis disruption, cell cycle alterations and many other factors contributing to neuronal dysfunction (McGeer *et al.*, 1987; Selkoe, 2001; Arendt, 2002; Eikelenboom *et al.*, 2006). In addition, these molecular, structural, and functional changes are boosted by the individual differences in genetic background, environmental stimuli, lifestyle, and other factors. Essentially, any co-morbid factor that concomitantly reduces the number and density of neurons and synapses or increases neuronal vulnerability in the hippocampus and isocortex has the potential to accelerate the onset and progression of the clinical manifestations of AD (Peavy *et al.*, 2007). On the other hand, protective factors may stimulate energy metabolism, blood supply, glial activity, neuronal signalling and plasticity and in this way protect the brain from cognitive decline (Fig. 1). In this paper, we provide an overview of the major non-genetic and genetic risk factors potentially contributing to the development of Alzheimer's disease.

2. Non-genetic risk and protective factors

2.1. Non-genetic risk factors

A large quantity of epidemiological studies confirmed that some groups of people are more vulnerable to sporadic AD than the rest of the population. Multiple factors may influence the onset and progression of the disease. The main risk-increasing factors examined in epidemiological studies are associated with life history. Some of them, like hypertension, diabetes, and obesity may have genetic component, but particular genes involved and complex mechanisms of their interaction with other genes and environmental factors are not fully understood yet. Several authors propose that neurodegenerative diseases are not a result of single-hit event, but rather a several-step process involving genetic, epigenetic and environmental events (Bossy-Wetzel *et al.*, 2004; Coppede *et al.*, 2006).

Age as a main risk factor. The greatest known risk factor for AD is the increasing age. The likelihood of developing AD doubles at every five years after age 65. After age 85, the risk reaches nearly 50 percent (Evans *et al.*, 1989).

Hypertension as a long-term stress of the blood vessel endothelium and walls is an important risk factor for AD. High midlife systolic blood pressure increases probability of AD or vascular dementia in later age (Kivipelto *et al.*, 2001; Freitag *et al.*, 2006) and also increases load of neurofibrillary tangles (NFTs) and amyloid plaques (Petrovitch *et al.*, 2000). In hypertensive individuals, the higher density of amyloid plaques and NFTs was found in preclinical stages of AD (Sparks *et al.*, 1995). A hypertension participates in several types of the brain damage: angiopathy (blood vessel deformity), atherosclerosis and silent infarctions, reduced cerebral blood flow (reduced delivery of the oxygen and nutrients to the tissue), neuronal damage caused by ischemia and altered calcium homeostatic mechanism, changes in signaling pathways, and

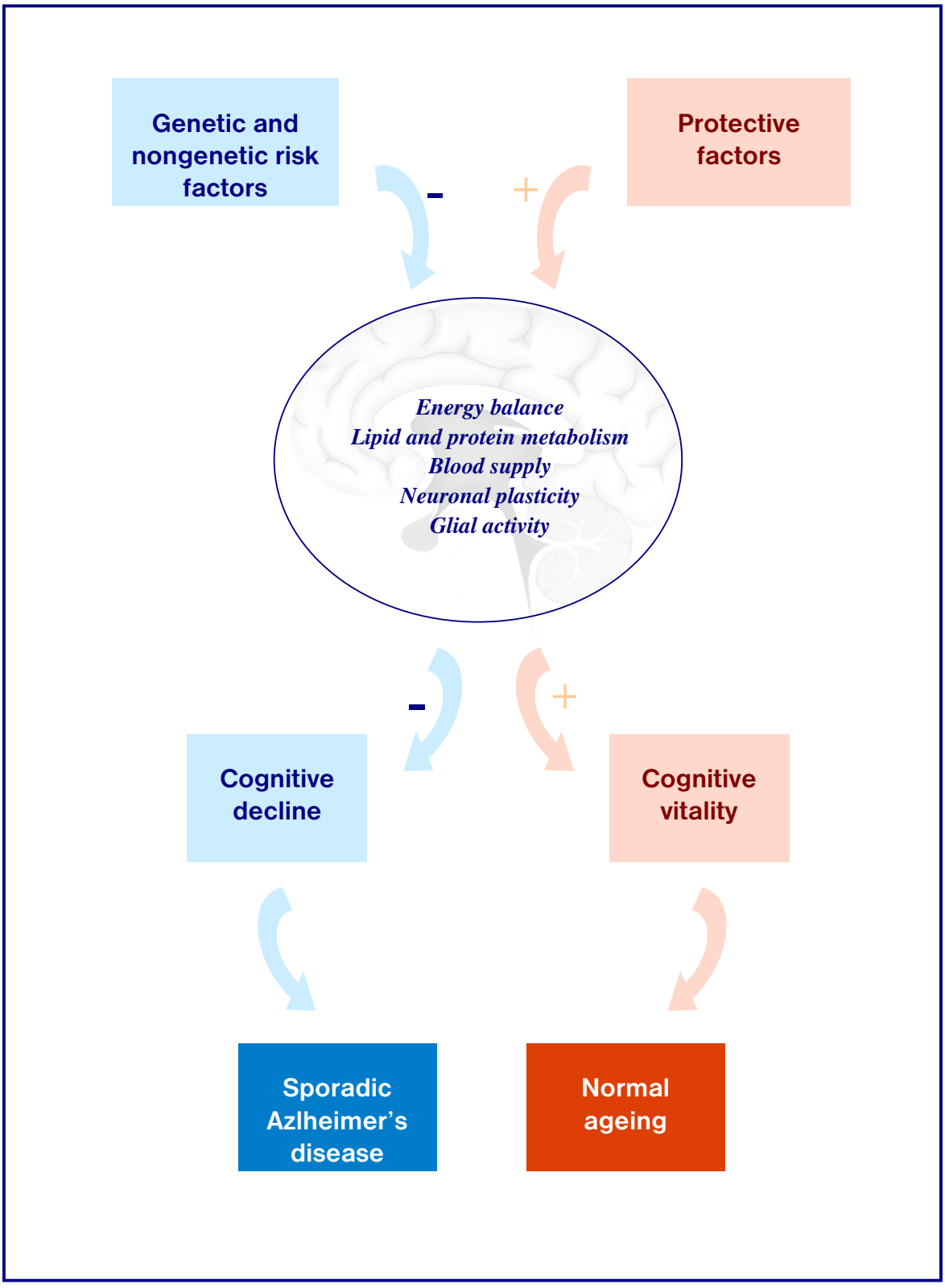

Fig. 1

Impact of risk and protective factors on the cognitive functions in humans

oxidative stress (Farkas *et al.*, 2000; Sabbatini *et al.*, 2001; Roman and Kalaria, 2006; Inzitari *et al.*, 2007; Lambeth, 2007).

Diabetes. Several epidemiological studies showed positive correlation between diabetes and AD (Breteler, 2000; Luchsinger *et al.*, 2007a). Supposed mechanism contributing to the neurodegeneration could comprise vascular changes in diabetes or insulin deregulation itself. Insulin plays an important role not only in energy metabolism, but also in memory function (insulin-sensitive glucose transporters are localised to the memory supporting brain regions) (Watson and Craft, 2003). Some studies showed that noradrenaline levels are increased in CSF after induced peripheral hyperinsulinemia. This increase correlates with the improved memory in healthy adults (Watson *et al.*, 2006). Furthermore, insulin deregulation may contribute to the AD pathology by decreased glucose utilisation, increased oxidative stress through the formation of advanced glycation end-products, increased tau phosphorylation and amyloid beta (Aβ) aggregation (Grossman, 2003). Insulin degrading enzyme (IDE), capable to clean-up beta amyloid from the brain, has higher preference for insulin than for amyloid (Taubes, 2003). Therefore, in the case of hyperinsulinemia, insulin depletes the capacity of the enzyme, enabling accumulation of amyloid. Moderate hyperinsulinemia can elevate inflammatory markers – interleukin 1 alpha (IL-1α), interleukin 1 beta (IL-1ß), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNFα) – and level of amyloid in the brain, thereby potentially increasing the risk of AD (Fishel *et al.*, 2005).

Neuroinflammation is a common denominator of many risk factors in AD. Multiple studies provided increasing evidence that inflammation plays an integral role in the development of AD. Despite the ongoing research, the extent to which neuroinflammation contributes to disease pathogenesis is still not fully understood (Žilka *et al.*, 2006). Several follow-up studies suggested that the inflammation precedes the development of the plaques, tangles, and clinical signs of dementia and that increased inflammatory markers might be another risk factor for AD. High serum levels of fibrinogen (non-specific inflammatory marker) increased the risk of AD and vascular dementia (van Oijen *et al.*, 2005). In elder people, higher serum levels of IL-1ß and TNFα were regarded as the markers of AD risk (Tan *et al.*, 2007). The Honolulu-Asia Aging study lasting for 25-year found the significant connection between non-specific inflammatory marker (high-sensitivity C-reactive protein) and the increased risk of AD and vascular dementia (Schmidt *et al.*, 2002).

Obesity in middle age (independently of other co-morbid factors) was strongly associated with the risk of AD in later life (Whitmer *et al.*, 2005). Adipose tissue is a potent source of inflammatory interleukins and other cytokines contributing to chronic inflammatory state, insulin resistance, and cardiometabolic risks linked to cognitive dysfunction. Several studies showed an impaired performance in memory and executive function tests in healthy obese adults, when compared to adults with normal body mass index. Memory impairment related to the obesity was independent of age (Gunstad *et al.*, 2006, 2007).

High cholesterol. In epidemiologic studies hypercholesterolemia appeared to be a risk factor for AD (Kivipelto *et al.*, 2001). This conclusion was confirmed by the experiments in mice, when high dietary intake of cholesterol caused increase of Aß accumulation (Refolo *et al.*, 2000). On the contrary, cholesterol-lowering drugs statins decreased the risk of AD (Wolozin *et al.*, 2000).

Total homocysteine (tHcy). Elevated tHcy level is considered as a risk factor for arteriosclerosis and cardiovascular diseases, but also as an independent risk factor for AD (Quadri *et al.*, 2004; Ravaglia *et al.*, 2005). Elevated tHcy in the plasma may supplement neurotoxic and vasculopathic processes including Aβ-protein metabolism. According some authors, it is not clear, if an elevation in tHcy concentration is a "risk factor" with a direct pathophysiological role in the development of the disease or merely a "risk marker" reflecting an underlying process such as oxidative stress responsible for both the high tHcy concentrations and the development of AD (Seshadri, 2006).

Reduced levels of gonadal hormones. Low free testosterone in men was determined as an independent risk factor for AD – and not a consequence of the disease (Hogervorst *et al.*, 2004; Zondermann, 2005). Association of estrogen level in women to the risk of AD is less perspicuous. Estrogen seems to protect neurons and improve cognition. However, a growing number of pregnancies increases the risk of developing AD. Nulliparous women are at lowest risk (Colucci *et al.*, 2006). Post-menopausal women are more susceptible to AD than men in the same age group. Preventive effect of the estrogen and/or progesterone hormone replacement therapy was not confirmed (Seshadri *et al.*, 2001; Rapp *et al.*, 2003). Some authors emphasize the role of luteinizing hormone (LH) rather than estrogen. Its levels increase with ageing and are higher in women with AD compared to healthy controls (Casadesus *et al.*, 2005; Webber *et al.*, 2005). In amyloid mouse model, LH ablation improved cognition and decreased Aß deposition (Casadesus *et al.*, 2006).

Viral infection is another risk factor connected to the inflammation and oxidative stress. More viruses infiltrate the brain in elderly people probably due to the decreasing efficacy of immune system, e.g. herpes simplex viruses type 1 (HSV-1) and type 6 (HSV-6), and cytomegalovirus (CMV). Interestingly, HSV-6 was found more frequently in AD patients than in controls (prevalence of 70% in AD patients versus 40% in controls) (Lin *et al.*, 2002). It is noteworthy that the process of HSV-6 penetration into the elderly human

brains is APOE allele independent, what is different from HSV-1. However, it is not clear whether HSV-6 is a risk factor by itself or its presence is rather a consequence of higher susceptibility of the AD brain to virus penetration. HSV-1 infection is common (90% of the population is carrying this virus) and the virus remains life-long in a latent state in peripheral neurons reaching the brain in older age. It was shown that HSV-1 recurrent infection in combination with APOE ε4 allele increases the risk of AD (Itzhaki *et al.*, 1997). In APOE transgenic mouse model, APOE genotype modulates neuroinvasiveness of the HSV-1, where APOE ε4 allows the virus entry into the CNS in higher titres (Burgos *et al.*, 2003). Another study in home-dwelling elderly found positive correlation between the increased viral burden (HSV-1 or CMV) and a cognitive impairment without any bacterial interference (Strandberg *et al.*, 2004). Finally, it was shown that the previous exposure to the conventional anti-viral vaccines (diphtheria or tetanus, poliomyelitis and influenza) decreases the risk of future AD (Verreault *et al.*, 2001).

Smoking increases the levels of reactive oxygen and nitrogen significantly, causes depletion of antioxidants, and damages cardiovascular system. On the other hand, the well-documented effect of nicotine on learning and memory via nicotinic acetylcholine receptors makes relation of smoking to AD ambiguous. Indeed, smoking in elderly increases the risk of AD more than two times – only in APOE ε4 carriers no association was found (Ott *et al.*, 1998). Other study showed that older smokers are more likely to develop AD compared to those who never smoked. Intriguingly, former smokers carrying APOE ε4 were less likely to develop AD than those APOE ε4 carriers who never smoked (Aggarwal *et al.*, 2006).

Chronic stress may contribute to the memory loss in people at risk for developing AD. Wilson *et al.* (2006) reported that persons more prone to stress suffered higher risk of developing AD and accelerated cognitive decline. Psychological stress affects the hypothalamic-pituitary-adrenal axis resulting in the sustained release of gluco-corticoids (cortisol). Prolonged increased cortisol levels caused reduction of hippocampal volume and deficit in hippocampus-dependent memory tasks in elderly humans (Lupien *et al.*, 1998). The interaction between APOE ε4 allele and chronic stress has not been understood yet. However, the synergic effect of the risk genotype and memory impairment caused by stress-increased cortisol levels was observed (Peavy *et al.*, 2007).

Head injury has several common links to AD, e.g. blood-brain barrier damage with leakage of plasma proteins, toxins, and viruses into the brain, free radical release, an axonal damage together with neuronal loss lower a threshold for the dementia onset. Although some authors consider brain injury contribution to AD pathogenesis controversial, many clinical studies and experiments in animal models showed that repetitive, but also single head injury was a risk factor for AD (Lye and Shores, 2000; Szczygielski *et al.*, 2005). An autopsy study confirmed the clinical studies suggesting some influence of severe traumatic brain injury on the development of AD (Jelinger *et al.*, 2001).

Environmental exposure to metals was studied due to the high capability of brain to accumulate metals that led to the protein damage and aggregation and contributed to an increased oxidative stress. Thus, homeostasis of some metals is altered in AD patients. Studies examining the influence of aluminium, zinc, copper, iron or mercury in relation to neurodegeneration have conflicting results and influence of these metals on the risk of AD is still discussed (Coppede *et al.*, 2006).

2.2 Non-genetic protective factors

Epidemiological studies have suggested that an active engagement in social, mental and physical activities may postpone the onset of dementia by providing a cognitive reserve or by reducing psychosocial stress (Qiu *et al.*, 2007).

Intellectual stimulation and social interaction. Higher IQ, educational level or occupational attainment decreases the risk of AD development (Colucci *et al.*, 2006; Mortimer *et al.*, 2005). Most studies explain this relationship by the cognitive reserve that inhibits some clinical signs of AD in spite of the relatively developed pathology in the brain. Cognitive reserve may be based on a more efficient utilization of brain networks or an ability to recruit alternate brain networks as needed, what may be intentionally directly enhanced (Stern, 2006). In elderly, social isolation deprives individual of the important stimuli. In a 4-year follow-up study, social isolation was associated with a lower level of the cognition at baseline, more rapid decline and development of AD symptoms, but not with the load of AD histopathological hallmarks (Wilson *et al.*, 2007). This result suggests that the social interaction influences a cognitive reserve of the patient, capacity of the "healthy" neurons and functional outcome, but not the progression of pathological processes themselves.

However, challenging of neuronal plasticity by various environmental stimuli improves the neuronal environment, enhances neurogenesis, and reduces apoptosis. In several rodent models of neurodegeneration, it was possible to restrict the development of the brain pathology. In amyloid transgenic mice, the plaque burden was reduced in response to the enriched environment (Lazarov *et al.*, 2005).

Regular physical activity has positive effect on the cognitive functions not only by the means of beneficial effect on cardiovascular system with improvement of the energy and nutrient supply to the nerve tissue, but also by profound effect on the synaptic plasticity (Kramer *et al.*, 1999). Novel

findings suggest that an exercise may induce a variety of molecular factors involved in angiogenesis and neurogenesis including brain-derived neurotrophic factor, insulin-like growth factor I, and vascular endothelial growth factor (Gomez-Pinilla, 2007; Kramer and Erickson, 2007). Physical exercise reduces risk of AD in elderly and delays its onset (Laurin *et al*., 2001; Larson *et al*., 2006). In the patients already suffering of AD, exercise can improve mood, condition, and cognitive functions (Arkin, 2003). Low physical activity increases the risk of AD in future (Wang *et al.*, 2006).

Benefits of *vitamin-rich diet* are associated with the reduction of oxidative stress (antioxidative actions of vitamins C, E) and cell membrane protection (vitamin E). Vitamins B1 and B9 improve cognitive functions in elderly. B6 and B12 are directly involved in the synthesis of neurotransmitters (Bourre, 2006a). Higher intake of folate decreases the risk of AD probably through the lowering of homocysteine levels (Luchsinger *et al.*, 2007b).

An optimal intake of nutrients does not protect people from dementia. However, inadequate dietary habits widespread in population of the developed countries result in a subclinical deficiency of essential nutrients and increase the risk of age-related disorders (Salerno-Kennedy and Cashman, 2005).

Omega-3 fatty acids (family of polyunsaturated fatty acids, PUFAs) are important for memory and cognition, neuroplasticity of nerve membranes, synaptogenesis, and synaptic transmission. Docosahexaenoic acid is essential for the synthesis of membrane structures and for neuronal functions (Bourre, 2006b). The ratio of omega-3 to omega-6 PUFAs can be modulated by the dietary intake. This ratio influences a neurotransmission and prostaglandin formation, which are processes vital in the maintenance of normal brain function (Haag, 2003). The signs of omega-3 fatty acid deficit were found in neurodegenerative disorders as the AD and schizophrenia (Saugstad, 2006). Dietary supplement of omega-3 fatty acids helped to slow down the progression of cognitive impairment only in patients with very mild AD symptoms (Freund-Levi *et al.*, 2006). In addition, the Rotterdam study found that low intake of PUFAs and high intake of total and saturated fats was not associated with the risk of dementia (Hofman *et al.*, 2006).

Epidemiological evidence indicates that *non-steroidal anti-inflammatory drugs* (NSAIDs) may lower the risk of developing AD (Tuppo and Arias, 2005). Since patients with rheumatoid arthritis and osteoarthritis are usually treated with NSAIDs for a long period of time, epidemiological studies have looked into the association of these diseases and AD. Many of those studies have reported an inverse relationship between having arthritis (and being treated with NSAIDs) and AD (Zandi and Breitner, 2001), but not with the vascular dementia (McGeer and McGeer, 2007). Unlike promising results coming from small-scale trials, later large-scale clinical studies of NSAIDs in AD patients have been disappointing. Randomized controlled trials, assessing the effect of the COX-1 and COX-2 inhibitors, failed to demonstrate any beneficial effects on cognition, behavior or activities of daily livings of AD patients (McGeer and McGeer, 2007). Among the reasons of anti-inflammatory therapy failure is the possibility that by the time the AD becomes clinically significant, the neuropathology of the brain is very advanced for NSAID therapy to be effective. These data provide perhaps the most convincing evidence to date that NSAIDs may be useful in the prevention rather than in therapy of AD (Žilka *et al.*, 2006).

Long-term treatment by cholesterol-lowering drugs *statins* (3-Hydroxy-3-Methyglutaryl Coenzyme A reductase inhibitors) is supposed to reduce the risk of AD. There are more mechanisms proposed, e.g. suppression of beta-amyloid metabolism, vascular effects, and antiinflammatory effects. Wolozin *et al.* (2000) showed that the patients treated by the statins had lower prevalence of diagnosed AD, but only in the group of patients younger than 80 years (Rockwood *et al.*, 2002). However, any beneficial effect of regular statin use on AD was not demonstrated (Zhou *et al.*, 2007).

3. Genetic risk factors

Over the last several years, hundreds of reports claimed or refuted genetic association with putative genes determining AD susceptibility. AD genetic studies detected more than 1000 different polymorphisms in 355 genes (Bertram *et al*., 2007). However, many genes potentially associated with the sporadic AD were not confirmed as candidate genes indicating an enormous genetic heterogeneity across populations. Here, we report several candidate genes involved in various disease-pathways that are associated with risk of AD (Table 1).

3.1. Apolipoprotein E variability – the main genetic risk factor

ApoE is a plasma cholesterol and phospholipid transporter that plays a central role in the lipoprotein metabolism in the brain and is involved in a repair, growth, and maintenance of myelin and neuronal membranes during development or after injury. Human ApoE exists in three major isoforms (E2, E3, and E4) encoded by distinct alleles (ε2, ε3, and ε4). APOE ε3 is the most frequent form (78%), APOE ε4 makes up 15% and APOE ε2 approximately 7% (Corder *et al.*, 1994). The APOE ε4 allele is the main genetic risk factor for the development of sporadic AD, whereas the ε3 and ε2 alleles provide relative protection from this neurodegenerative disorder (Farrer *et al.*, 1997).

Table 1. Genes and their polymorphisms in relation to the risk of AD

Gene	Relevance of the gene product for AD pathogenesis	Location	Polymorphism	Study
ABCA1	cholesterol efflux pump in lipid removal pathway	9q31.1	rs4149313 (I883M)	Katzov *et al*. (2004)
ACE	blood pressure regulation, fluid-electrolyte balance	17q23.3	rs1799752 (intron 16 ins/del)	Kehoe *et al*. (1999)
ACT	protects the tissue from proteolytic enzymes; component of plaques	14q32.1	ACT promoter, rs4934 (Ala-17Thr)	Licastro and Chiappelli (2003)
APOC1	potent inhibitor of LPL-mediated triglyceride lipolysis	19q13.2	rs11568822 (ins/del-HpaI)	Retz *et al*. (2001)
APOE	plasma cholesterol and phospholipid transporter with central role in brain lipoprotein metabolism	19q13.2	ε2/3/4	Corder *et al*. (1994)
BDNF	neuroptorection	11p13	C270T	Kunugi *et al*. (2001)
CST3	cysteine protease inhibitor, connected to atherosclerosis and vascular disease	20p11.21	rs1064039 (A25T)	Goddard *et al*. (2003)
CYP46A1	major cholesterol metabolizing enzyme	14q32.1	rs754203 (2i)	Li *et al*. (2006)
DNMBP	protein influencing cell junction formation	10q24.2	rs11190302	Kuwano *et al*. (2006)
ESR1	estrogen receptor	6q25.1	rs2234693 (PvuII), rs9340799 (XbaI)	Corbo *et al*. (2006)
HLA	major histocompatibility complex; key role in antigen presenting	6p21.3	HLA (A2)	Ballerini *et al*. (1999)
CH25H	supression of transcription of cholesterol synthetic enzymes	10q23	rs13500	Papassotiropoulos *et al*. (2005)
CHRNB2	subunit of nicotininc cholinergic receptor	1q21.3	rs4845378	Cook *et al*. (2004)
IDE	insulin degrading enzyme; ability to cleave amyloid beta	10q23-q25	rs3758505 (IDE_1)	Bian *et al*. (2004)
IL-10	anti-inflammatory cytokine	1q31-q32	rs1800871 (-819), rs1800896 (-1082)	Arosio *et al*. (2004)
IL-1A	pro-inflammatory cytokine	2q14	rs1800587 (-889)	Grimaldi *et al*. (2000)
IL-6	pro-inflammatory cytokine	7p21	rs1800795 (G-174C)	Licastro *et al*. (2003)
LPL	enzyme transporting cholesterol to neurones	8p22	rs268 (N291S), rs328 (S447Ter)	Baum *et al*. (1999)
MAPT	main NFT component	17q21.1	tau H1/H2	Myers *et al*. (2005)
NCSTN	regulation of Aβ production	1q22-q23	rs122239747 (L212L)	Confaloni *et al*. (2003)
PRNP	suggested function in: adhesion, transmembrane signaling, uptake of extracellular ligands	20p13	rs1799990 (M129V)	Golanska *et al*. (2004)
SORL1	role in generation of amyloid beta, through the recycling of APP	11q23.2-q24.2	rs1010159	Rogaeva *et al*. (2007)
TFAM	mitochondrial transcription factor, participates in mitochondrial genome replication	10q21	rs1937 (S12T), rs2306604	Günther *et al*. (2004)
TGFß	multifunctional cytokine controlling cell cycle, differentiation, apoptosis	19q13.2; 19q13.1	rs1800469 (-509)	Luedecking *et al*. (2000)
TNFα	pro-inflammatory cytokine	6p21.3	rs1800629 (-308)	Ramos *et al*. (2006)
UBQLN1	modulation of APP trafficking	9q22; 9q21.2-q21.3	rs12344615 (UBQ_8i)	Kamboh *et al*. (2006)

Compared with APOE ε2 and ε3, APOE ε4 increases the risk of cognitive impairments, lowers the age of onset of AD and decreases the response to AD treatments (Reed *et al.*, 1994). Moreover, APOE variability influences amyloid load and NFT density in AD patients. The APOE ε4 carriers have more plaques and tangles, than the carriers of the other APOE alleles (Nagy *et al.*, 1995). Another histopathological study showed that amyloid angiopathy was clearly related to frequency of APOE ε4 allele, although APOE relation to senile plaque load was weak (Berg *et al.*, 1998).

Although reports of the influence of APOE genotype on the quantity of amyloid and tau pathology in AD patients yielded contradictory results, Beffert and Poirier (1996) confirmed the relationship, but Landen *et al.* (1996) did not verify these results. It is likely that APOE genotype influences the neuronal plasticity. In AD cases without APOE ε4 allele, dendritic length and arborization were indistinguishable from the elderly controls in transentorhinal area, entorhinal cortex and subiculum/CA1, while AD cases carrying one or two APOE ε4 alleles showed regressive changes of the dendritic tree (Arendt *et al.*, 1998). Furthermore, loss of the synaptic proteins is more severe in patients with APOE ε4 allele (Tannenberg *et al.*, 2006). These findings were confirmed by the study with transgenic mice expressing human ApoE isoforms, when APOE ε4 impaired hippocampal plasticity and specifically blocked the environmental stimulation of synaptogenesis and memory, after the exposure to the enriched environment (Levi *et al.*, 2003).

Besides APOE, also polymorphism of apolipoprotein C-I gene promoter (AOPC1, chromosome 19, potent inhibitor of LPL-mediated triglyceride lipolysis) was studied for its possible relationship to AD. APOC1 allele A2 is closely linked to the APOE allele ε4 and might modulate the risk for AD (Retz *et al.*, 2001; Ki *et al.*, 2002). On the other hand, studies performed in African-Americans excluded the influence of APOC1 polymorphism (Tycko *et al.*, 2004).

In spite of the fact that APOE is the most important genetic risk factor for the late onset AD (accounting for nearly 30% of risk), APOE ε4 allele is neither necessary nor sufficient for the development of AD (Kamboh, 2004). About half of the AD patients have APOE ε3 homozygous genotype (Kuwano *et al.*, 2006). Therefore, there is constant search for other genetic risk factors having higher correlation with the onset and progression of AD. Many different candidate genes are under consideration. The results of multiple studies are summarized for meta-analysis in the AlzGene database (Bertram *et al.*, 2007). The strongest evidence for putative sporadic AD-linked genes was found on chromosomes 12, 10, 9 and 6 (Kamboh, 2004).

3.2. Genes connected to cholesterol metabolism

Several studies have provided convincing evidence that different aspects of brain lipid metabolism may influence Alzheimer disease pathogenesis. Therefore, several candidate genes became subject of epidemiological studies.

ATP-binding cassette transporter 1 (ABCA1) gene. Product of this gene is a membrane-associated protein that functions as a cholesterol efflux pump in the cellular lipid removal pathway. In AD patients, two ABCA1 gene haplotypes (H2, H5) were enriched, whereas two other common haplotypes in the studied region (H1, H3) were significantly under-represented (Katzov *et al.*, 2004; Chu *et al.*, 2007). In contrast, study of Shibata *et al.* (2006) did not support the hypothesis that ABCA1 gene was associated with susceptibility to AD.

Cholesterol 24-hydroxylase (CYP46A1) gene. Increasing biological findings argue for the importance of CYP46A1 in cholesterol homeostasis in cerebral structures. The studies among Chinese population supported the involvement of the polymorphism IVS3-128 and intron 2 polymorphism of CYP46A1 gene in the pathogenesis of AD (Ma *et al.*, 2006; Li *et al.*, 2006). However, other results did not support a genetic association between the intron 2 polymorphism of CYP46 gene and the risk of sporadic AD (Wang and Jia, 2007).

Cholesterol 25-hydroxylase (CH25H) gene. The microsomal enzyme CH25H is a high-density lipoprotein binding related protein and regulating lipid metabolism (Riemenschneider *et al.*, 2004). The CH25H gene showed high expression in vulnerable brain regions of AD patients. Authors suggested the possibility that CH25H polymorphisms are associated with different rates of brain Aβ deposition (Papassotiropoulos *et al.*, 2005). However, other studies stated that genetic variations do not contribute to the genetic risk of AD (Riemenschneider *et al.*, 2004; Shibata *et al.*, 2006).

Lipoprotein lipase (LPL) gene. LPL is an enzyme important for the lipid metabolism. It helps transfer lipids from lipoprotein particles into the cells. LPL binds ApoE lipoprotein particles and low-density lipoprotein receptor-related protein**,** an ApoE receptor. In the AD brain, LPL is present in amyloid plaques (Baum *et al.*, 1999). While few studies on clinically diagnosed subjects showed that LPL mutations were associated with altered AD risk (Baum *et al.*, 1999; Scacchi *et al.*, 2004), others did not support associations between AD and common polymorphisms in LPL (Martin-Rehrmann *et al.*, 2002; Fidani *et al.*, 2002; Riemenschneider *et al.,* 2004).

3.3. Amyloid metabolism genes

There are investigated many genes linked to amyloid production:

Alpha-1-antichymotrypsin (ACT) gene. ACT is an acute phase protein and plasma protease inhibitor supposed to protect the tissue from proteolytic enzymes. It is a component of the amyloid plaques and can bind amyloid peptide promoting its assembly and deposition (Potter *et al.*, 2001). A calcium-activated serine proteinase similar to cathepsin G may be involved in the generation of Aβ and may be a substrate for the ACT found in the brain (Kalashker, 1996). Increased levels of ACT have been widely reported in the cerebrospinal fluid and serum of AD patients. In addition, ACT mRNA is over-expressed in the grey matter of AD patients. In the ACT gene, a single nucleotide polymorphism identified in the signal peptide region seems to be important as a predisposing marker for AD in association with the APOE ε4 genotype (Licastro and Chiappelli, 2003).

Cystatin C (CST3) gene. Product of this gene is a cysteine protease inhibitor found in high concentrations in biological fluids and in all organs of the body. CST3 is known as an amyloidogenic protein and a component of the amyloid plaque (Goddard *et al.*, 2004). Furthermore, CST3 might play a role in the atherosclerotic and vascular disease. Recently, there was reported a positive relationship of the CST3 gene polymorphism to the risk of AD in European and Asian population (Goddard *et al.*, 2004; Cathcart *et al.*, 2005; Chuo *et al.*, 2007). The CST3-A allele was seen as an accumulation risk factor for early onset of AD. Moreover, a synergistic association among the CST3-A allele, APOE ε4 and AD was found in patients between 60 and 74 years (Beyer *et al.,* 2001). In contrast, other studies do not support these findings (Monastero *et al.*, 2005).

Insulin degrading enzyme (IDE) gene. IDE is a large zinc-binding protease of the M16A metalloprotease subfamily cleaving multiple short polypeptides that vary considerably in sequence. The ability to cleave Aß into non-toxic and non-depositing products makes IDE interesting for AD research (Suh and Checler, 2002). Moreover, IDE knock-out mice showed increased blood insulin and increased accumulation of amyloid precursor protein (APP) and ß-amyloid in the brain (Farris *et al.*, 2003). The IDE gene represents a strong positional and biologic candidate for late onset AD susceptibility. Among the four polymorphisms of IDE gene studied on Chinese population, only the C allele of single-nucleotide polymorphism IDE2 showed an association with AD. However, the association between IDE2 and AD was confined to APOE ε4 carriers only suggesting a possible synergic interaction between IDE and APOE ε4 in the risk to develop late-onset AD (Bian *et al.*, 2004). In contrast, other study indicated that variability in IDE gene might affect AD severity rather than risk (Blomqvist *et al.*, 2005).

Nicastrin (NCSTN) gene. Nicastrin is a type I transmembrane glycoprotein, an integral component of the multimeric gamma-secretase complex involved in the regulation of Aß production. Some differences were found in the distribution of genotype alterations in the AD patients compared to the controls (Confaloni *et al.*, 2003). In reverse, other study did not report any associations between NCSTN gene polymorphism, presenilins, Aß, and APOE genotype, or risk of AD (Orlacchio *et al.*, 2002).

Sortilin related receptor (SORL1) gene. This receptor plays a role in generation of Aβ, through the recycling of amyloid precursor protein. Ablation of SORL1 expression in knock-out mice causes increase of the Aβ levels (Andersen *et al.*, 2005). Rogaeva *et al.* (2007) reported that inherited variants in the SORL1 were associated with late onset of AD.

Ubiquilin (UBQLN1) gene. Ubiquilin (ubiquitin-like protein) influences the function of presenilin proteins involved in early onset of AD. The genetic variation in the UBQLN1 gene may have a modest effect on risk, age-at-onset and disease duration of AD. One common haplotype (H4) was associated with AD risk, while one less common haplotype (H5) was associated with protection (Kamboh *et al.*, 2006). Other authors point at the lack of association between ubiquilin gene variability and risk of the sporadic AD (Smemo *et al.*, 2006; Slifer *et al.*, 2006).

3.4. Tau protein gene

Tau protein gene mutations are involved in the frontotemporal dementia and Parkinson's disease linked to chromosome 17 (FTDP 17). However, the role of tau protein gene polymorphism in AD remains unidentified.

Microtubule associated protein tau (MAPT) gene. The main role of tau is to regulate the stabilization of microtubules that are determinants of the cellular morphology and serve as a track for microtubule based transport mechanisms. Significant relation between tau H1c haplotype and risk of AD was reported (Myers *et al.*, 2005). However, Mukherjee *et al.* (2007) did not confirm relation of H1c to the sporadic AD. Bullido *et al.* (2000) showed that G allele of tau gene (in biallelic polymorphism at position +34 of intron 11) in carriers of APOE ε4 allele increased risk of AD fivefold. Nevertheless, other studies showed no association between tau H1/H2 haplotypes and AD risk (Baker *et al.*, 2000; Russ *et al.*, 2001).

3.5. Inflammatory factors

Human leukocyte antigen (HLA) genes. Major histocompatibility complex (MHC) is a cluster of genes on a single chromosome. There are several gene loci and many alleles for class I and class II MHC proteins. MHC proteins are surface receptors with the primary function to present antigens and elicit immune response through T-cells. Many of the genetic variants of MHC II genes (HLA-DR) were identified as the risk factors in diseases such as diabetes and rheumatoid arthritis. Ballerini *et al.* (1999) reported that HLA A2 and ε4 alleles in Italian population may have additive effects on AD onset and that A2 (variant of a Class I MHC antigen-binding transmembrane protein) may play an important role in determining or contributing to a very early age at onset. However, Small *et al.* (1999) found no association between A2 allele and AD. Other study found relationship of A2 allele to increased risk of AD in Scottish population, but not to the onset age (Harris *et al.*, 2000). HLA B27 allele is related to the increased risk of AD especially for homozygotes (Lehmann *et al*., 2006). Curran *et al.* (1997) found increased risk of AD in patients with DR1, DR2 and DR3 antigens (MHC II). DR4 and DR6 antigens were associated with decreased risk.

Interleukin 1A (IL-1A) gene. IL-1 is a pluripotent cytokine overexpressed by microglial cells within affected cerebral cortical regions of the AD brain and may contribute to reorganisation of cytoskeleton, synaptic loss, tau phosphorylation and neurofibrillar pathology (Li *et al*., 2003). Grimaldi *et al.* (2000) found strong association between the IL-1A –889T/T genotype and earlier time of AD onset. C/C genotype carriers showed onset of the disease 9 years later. Other studies found no relationship between IL-1A variability and AD risk (Prince *et al.*, 2001; Fidani *et al.* 2002).

Interleukin 6 (IL-6) gene. Cytokine IL-6 mediates cell growth, differentiation and neuronal degeneration. An elevated level of IL-6 was detected in brain homogenates and peripheral blood of AD patients suggesting its role in AD pathogenesis.

The –174 C allele in the promoter region of IL-6 gene was over-represented in AD patients compared to the controls and significantly increased the risk of AD. Moreover, the –174 C/C genotype was associated with a high risk of the disease in women (Licastro *et al.*, 2003). However, van Oijen *et al.* (2006) in the Rotterdam study found no relationship between IL-6 –174 G/C polymorphism and AD risk.

Interleukin 10 (IL-10) gene. IL-10 produced mainly by monocytes is an anti-inflammatory cytokine. IL-10 is over-expressed in AD patients suggesting its protective role against neuron damage (Lio *et al*., 2006b). Positive association between the –819 T/C and –1082 G/A polymorphism and AD risk associated with a low production of anti-inflammatory cytokine IL-10 has been considered as an additive and independent genetic risk factor for AD (Arosio *et al*., 2004; Bagnoli *et al.*, 2007).

Transforming growth factor beta (TGFβ) gene. TGFß is a multifunctional cytokine that controls cell cycle, differentiation, apoptosis and other functions in many cell types. Dysfunction of TGFß signaling was observed in AD. Study performed by Luedecking *et al.* (2000) suggested that –509 C/T polymorphism of TGFß1 may be modestly associated with the risk of AD. This finding was supported by Dickson *et al.* (2005), whereas other studies showed no involvement of TGFß polymorphisms in the development of AD (van Oijen *et al.*, 2006; Araria-Goumidi *et al.*, 2002).

Tumor necrosis factor alpha (TNFα) gene. TNFα is a cytokine involved in the regulation of a wide spectrum of biological processes including inflammation, cell proliferation, differentiation, apoptosis, and lipid metabolism. TNFα is believed to trigger a programmed cell death in the periphery (Venters *et al*., 2000), while within CNS it may have neuroprotective effect (Ferenčík *et al.*, 2001). In the brain TNFα may mediate synaptic scaling in response to a prolonged blockade of activity (Stellwagen and Malenka, 2006). Increased levels of TNFα in AD patients may represent compensatory mechanism of the brain against a progressive synaptic loss. The levels of this cytokine did not differ significantly in AD patients displaying different alleles of the TNF gene (Tarkowski *et al.*, 2000). Author suggests that the increased production of TNFα in AD patients is preferentially controlled by an environmental stimulus rather than by a genetic makeup.

Variation in the TNFα promoter region (–863 A allele) may affect cerebral inflammatory response and the risk of late-onset AD (Ramos *et al*., 2006). In contrast, Fung *et al.* (2005) did not show significant difference in genotype distribution in Taiwanese population (TNFα –1031 T/C, –863 C/A and –857 C/T polymorphisms) between the AD cases and controls.

However, two independent studies reported that genetic variation at TNFα (–308 A/G polymorphism) modulates the AD onset age and carriers of –308 A showed a significantly lower mean age at onset than non-carriers of this allele. This difference was more evident, when ApoE status was taken into account (Alvarez *et al.*, 2002; Lio *et al.*, 2006a).

3.6. Other possible genetic risk factors

Other investigated genes are involved in different functional pathways including blood pressure regulation, neuronal signalling, and plasticity.

Angiontensin I converting enzyme (ACE) gene. This enzyme catalyzes the conversion of angiotensin I into a physiologically active angiotensin II and plays a key role in the regulation of blood pressure. Numerous studies examined the relationship of ACE gene variability and risk of AD. Several studies reported a positive association (Kehoe *et al.*, 1999, 2003; Alvarez *et al.*, 1999; Richard *et al.*, 2001), but other found no relationship between the ACE gene variability and AD risk (Narain *et al.*, 2000; Seripa *et al.*, 2003).

Brain-derived neurotrophic factor (BDNF) gene. BDNF promotes the survival of the neuronal populations and regulates the synaptic transmission and plasticity at adult synapses in many regions of the CNS. The levels of BDNF are reduced in the specific brain regions during AD and BDNF gene polymorphisms have been suggested to influence AD risk. Positive relationship was found between the single nucleotide polymorphism C270T and sporadic AD risk (Kunugi *et al.*, 2001) especially in patients lacking APOE ε4 allele (Riemenschneider *et al.*, 2002). This finding was confirmed later by Matsushita *et al.* (2005) showing the significant involvement of polymorphisms G196A and C270T on BDNF gene. In contrast, other studies performed in different populations showed completely different results (Desai *et al.*, 2005).

Dynamin-binding protein (DNMBP) gene. This gene is linked to regulation of the actin cytoskeleton and control of cell junction formation. Recently, three single nucleotide polymorphisms on DNMBP gene were found to correlate with late-onset of AD in Japanese population (Kuwano *et al.*, 2006). In contrast, the study performed on Caucasian American population showed no correlation between the single nucleotide polymorphism of DNMBP gene and AD risk (Minster *et al.*, 2007).

Nicotinic acetylcholine receptor ß2 subunit (CHRNB2) gene. The product of this gene is a component of cholinergic signalling pathway that is directly associated with cognition. Knock-out mice experiments revealed that CHRNB2 contributed to the complex cognitive functions (Granon *et al.*, 2003) and played an important role in regulation of hippocampal neurons proliferation (Harrist *et al.*, 2004). The cholinergic deficit is one of the most conspicuous AD symptoms (Levin *et al.*, 2006). A significant association of a non-coding polymorphism in CHRNB2 and AD was

observed (Cook *et al.*, 2004), but further examination of large case-control series are needed.

Estrogen receptor alpha (ESR1) gene. Estrogen nuclear receptor ESR1 is a DNA-binding transcription factor that mediates the actions of estrogen. Several studies showed that different ESR1 polymorphisms might influence the cognitive function test performance in women (Kravitz *et al.*, 2006; Olsen *et al.*, 2006). In AD, expression of ESR1 is increased in nucleus basalis of Meynert neurones, is the major source of cholinergic innervation in neocortex (Ishunina and Swaab, 2001). ESR1 polymorphism could account for the variability observed in an estrogen treatment outcome. It was confirmed that ESR1 variability modulated the susceptibility to AD in Asian individuals, but not in Europeans (Luckhaus and Sand, 2007). ESR polymorphisms (PvuII and XbaI) interactions with ApoE polymorphism and plasma ApoE levels were also studied. ESR1 PP and XX genotypes were associated with an increased risk for AD in males only and conferred a relevant additional risk of AD to subjects carrying APOE ε4 allele. Authors suggest that the involvement of ESR1 polymorphisms in AD onset is mediated by the regulation of APOE expression. ESR1 polymorphisms are also associated with a faster cognitive decline in the women AD patients (Corbo *et al.*, 2006).

Prion protein (PRNP) gene. Product of this gene is a membrane glycosylphosphatidylinositol-anchored glycoprotein with an unknown function. It has been suggested that prion protein could play an important role in adhesion, transmembrane signalling and uptake of extracellular ligands. Several authors stated that homozygous MM or VV genotype represented a risk factor for AD (Golanska *et al.*, 2004; Gacia *et al.*, 2006). However, other studies (Combarros *et al.*, 2000; Ohkubo *et al.*, 2003; Li *et al.*, 2005) failed to reveal any relationship between the PRNP polymorphism and the risk of AD.

Transcription factor A, mitochondrial (TFAM) gene. TFAM is essential for transcription of mammalian mitochondrial DNA (mtDNA) and regulation of mtDNA copy number. Mitochondrial dysfunction may underlay neurodegeneration in AD and for that reason, several studies were engaged in the genetic study of TFAM gene polymorphisms as a risk factor for sporadic AD. Indeed, some studies described an association between the TFAM gene variability and risk of AD (Günther *et al.*, 2004; Belin *et al.*, 2007).

4. Conclusion

Sporadic AD is a multifactorial neurodegenerative disorder arising from a number of different, but related biological alterations that contribute to the pathogenesis of the disease. Several genes involved in the various metabolic pathways were presented as the genetic risk factors in AD. The majority of these genes may influence the vulnerability of the central nerve system without direct impact on the primary causes of AD. The genetic risk factors can not be influenced by a person, but the risk factors related to diet and life style can be changed before the person becomes a patient. A set of currently known inter-connected risk factors (cardiovascular diseases, hypercholesterolemia, diabetes type 2 and obesity) is sufficient for at least rough outline of basic program for protection of the brain's health until senescence and to prevent AD or restrain its impact on patient, his relatives and society.

Diversity of the AD risk and protective factors shows that almost any external or metabolic influence disturbing homeostasis of the neuronal environment and function can accelerate progress of the long-running neurodegenerative process or decrease the capacity of the brain to resist the disease. This relationship allows the proposition that almost any therapeutic action improving neuronal environment or function may modify the progression of the disease.

Finally, novel therapeutic approaches seem to be focused on the personalized treatment with consideration of patient's genetic features and environmental exposures. Therefore, the study of the mutual relationship between environmental stimuli and genetic background may be crucial to achieve the most effective treatment.

Acknowledgements. This study was supported by the grant 2/5101/26 from the Scientific Grant Agency of Ministry of Education and Slovak Academy of Sciences and by the grants APVV 0363-06 and APVV 0603-06 from the Slovak Research and Development Agency.

References

Aggarwal NT, Bienias JL, Bennett DA, Wilson RS, Morris MC, Schneider JA, Shah RC, Evans DA (2006): The relation of cigarette smoking to incident Alzheimer's disease in a biracial urban community population. *Neuroepidemiology* **26**, 140-146.

Alvarez R, Alvarez V, Lahoz CH, Martínez C, Peña J, Sánchez JM, Guisasola LM, Salas-Puig J, Morís G, Vidal JA, Ribacoba R, Menes BB, Uría D, Coto E (1999): Angiotensin converting enzyme and endothelial nitric oxide synthase DNA polymorphisms and late onset Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry* **67**, 733-736.

Alvarez V, Mata IF, Gonzales P, Lahoz CH, Martinez C, Pena J, Guisasola LM, Coto E (2002): Association between the TNFα-308 A/G Polymorphism and the Onset-Age of Alzheimer Disease. *Am. J. Med. Genet. (Neuropsychiatric Genetics)* **114**, 574-577.

Andersen OM, Reiche J, Schmidt V, Gotthardt M, Spoelgen R, Behlke J, von Arnim CA, Breiderhoff T, Jansen P, Wu X, Bales KR, Cappai R, Masters CL, Gliemann J, Mufson

EJ, Hyman BT, Paul SM, Nykjaer A, Willnow TE (2005): Neuronal sorting protein-related receptor sorLA/LR11 regulates processing of the amyloid precursor protein. *Proc. Natl. Acad. Sci. USA* **102**, 13461-13466.

Araria-Goumidi L, Lambert JC, Mann DM, Lendon C, Frigard B, Iwatsubo T, Cottel D, Amouyel P, Chartier-Harlin MC (2002): Association study of three polymorphisms of TGF-beta1 gene with Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry* **73**, 62-64.

Arendt T (2002): Dysregulation of neuronal differentiation and cell cycle control in Alzheimer's disease, *J. Neural Transm. Suppl.*, 77-85.

Arendt T, Bruckner MK, Gertz JH, Marcova J (1998): Cortical distribution of neurofibrillary tangles in Alzheimer's disease matches the pattern of neurons that retain their capacity of plastic remodelling in the adult brain. *Neuroscience* **83**, 991-1002.

Arkin SM (2003): Student-led exercise sessions yield significant fitness gains for Alzheimer's patients. *Am. J. Alzheimers Dis. Other Demen.* **18**, 159-170.

Arosio B, Trabattoni D, Galimberti L, Bucciarelli P, Fasano F, Calabresi C, Cazzullo CL, Vergani C, Annoni G, Clerici M (2004): Interleukin-10 and interleukin-6 gene polymorphisms as risk factors for Alzheimer's disease. *Neurobiol. Aging* **25**, 1009-1015.

Bagnoli S, Cellini E, Tedde A, Nacmias B, Piacentini S, Bessi V, Bracco L, Sorbi S (2007): Association of IL10 promoter polymorphism in Italian Alzheimer's disease. *Neurosci. Lett.* **418**, 262-265.

Baker M, Graff-Radford D, DeVrieze FW, Graff-Radford N, Petersen RC, Kokmen E, Boeve B, Myllykangas L, Polvikoski T, Sulkava R, Verkoniemmi A, Tienari P, Haltia M, Hardy J, Hutton M, Perez-Tur J (2000): No association between TAU haplotype and Alzheimer's disease in population or clinic based series or in familial disease. *Neurosci. Lett.* **285**, 147-149.

Ballerini C, Nacmias B, Rombola G, Marcon G, Massacesi L, Sorbi S (1999): HLA A2 allele is associated with age at onset of Alzheimer's disease. *Ann. Neurol.* **45**, 397-400.

Baum L, Chen L, Masliah E, Chan YS, Ng HK, Pang CP. (1999): Lipoprotein lipase mutations and Alzheimer's disease. *Am. J. Med. Genet.* **88**, 136-139.

Beffert U, Poirier J (1996): Apolipoprotein E, plaques, tangles and cholinergic dysfunction in Alzheimer's disease. *Ann. N.Y. Acad. Sci.* **777**, 166-174.

Belin AC, Björk BF, Westerlund M, Galter D, Sydow O, Lind C, Pernold K, Rosvall L, HÍkansson A, Winblad B, Nissbrandt H, Graff C, Olson L (2007): Association study of two genetic variants in mitochondrial transcription factor A (TFAM) in Alzheimer's and Parkinson's disease. *Neurosci. Lett.* **420**, 257-262.

Berg L, McKeel Jr DW, Miller JP, Storandt M, Rubin EH, Morris JC, Baty J, Coats M, Norton J, Goate AM, Price JL, Gearing M, Mirra SS, Saunders AM (1998): Clinico-pathologic studies in cognitively healthy aging and Alzheimer's disease: relation of histologic markers to dementia severity, age, sex, and apolipoprotein E genotype. *Arch. Neurol.* **55**, 326-235.

Bertram L, McQueen MB, Mullin K, Blacker D, Tanzi RE (2007): Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. *Nat. Genet.* **39**, 17-23.

Beyer K, Lao JI, Gomez M, Riutort N, Latorre P, Mate JL, Ariza A (2001): Alzheimer's disease and the cystatin C gene polymorphism: an association study. *Neurosci. Lett*. **315**, 17-20.

Bian L, Yang JD, Guo TW, Sun Y, Duan SW, Chen WY, Pan YX, Feng GY, He L (2004): Insulin-degrading enzyme and Alzheimer disease: a genetic association study in the Han Chinese. *Neurology* **63**, 241-245.

Blomqvist ME, Chalmers K, Andreasen N, Bogdanovic N, Wilcock GK, Cairns NJ, Feuk L, Brookes AJ, Love S, Blennow K, Kehoe PG, Prince JA (2005): Sequence variants of IDE are associated with the extent of beta-amyloid deposition in the Alzheimer's disease brain. *Neurobiol. Aging* **26**, 795-802.

Bossy-Wetzel E, Schwarzenbacher L, Lipton SA (2004): Molecular pathways to neurodegenration. *Nat. Med.* **10**, (Suppl.) S2-S9.

Bourre JM (2006a): Effects of nutrients (in food) on the structure and function of the nervous system: update on dietary requirements for brain. Part 1: micronutrients. *J. Nutr. Health Aging* **10**, 377-385.

Bourre JM (2006b): Effects of nutrients (in food) on the structure and function of the nervous system: update on dietary requirements for brain. Part 2: macronutrients. *J. Nutr. Health Aging* **10**, 386-399.

Breteler M (2000): Vascular risk factors in Alzheimer's disease: An epidemiologic perspective. *Neurobiol. Aging* **21**, 153-160.

Bullido MJ, Aldudo J, Frank A, Coria F, Avila J, Valdivieso F (2000): A polymorphism in the tau gene associated with risk for Alzheimer's disease. *Neurosci. Lett.* **278**, 49-52.

Burgos JS, Ramirez C, Sastre I, Bullido MJ, Valdivieso F (2003): ApoE4 is more efficient than E3 in brain access by herpes simplex virus type 1. *Neuroreport* **14**, 1825-1827.

Casadesus G, Atwood CS, Zhu X, Hartzler AW, Webber KM, Perry G, Bowen RL, Smith MA (2005): Evidence for the role of gonadotropin hormones in the development of Alzheimer disease. *Cell. Mol. Life Sci.* **62**, 293-298.

Casadesus G, Webber KM, Atwood CS, Pappolla MA, Perry G, Bowen RL, Smith MA (2006): Luteinizing hormone modulates cognition and amyloid-beta deposition in Alzheimer APP transgenic mice. *Biochim. Biophys. Acta* **1762**, 447-452.

Cathcart HM, Huang R, Lanham IS, Corder EH, Poduslo SE (2005): Cystatin C as a risk factor for Alzheimer disease. *Neurology* **64**, 755-757.

Chu LW, Li Y, Li Z, Tang AY, Cheung BM, Leung RY, Yik PY, Jin DY, Song YQ (2007): A novel intronic polymorphism of ABCA1 gene reveals risk for sporadic Alzheimer's disease in Chinese. Am. J. Med. Genet. B. *Neuropsychiatr. Genet.* (in press).

Chuo LJ, Sheu WH, Pai MC, Kuo YM (2007): Genotype and plasma concentration of cystatin C in patients with late-

onset Alzheimer disease. *Dement. Geriatr. Cogn. Disord.* **23**, 251-257.

Colucci M, Cammarata S, Assini A, Croce R, Clerici F, Novello C, Mazzella L, Dagnino N, Mariani C, Tanganelli P (2006): The number of pregnancies is a risk factor for Alzheimer's disease. *Eur. J. Neurol.* **13**, 1374-1377.

Combarros O, Sánchez-Guerra M, Llorca J, Alvarez-Arcaya A, Berciano J, Peña N, Fernández-Viadero C (2000): Polymorphism at codon 129 of the prion protein gene is not associated with sporadic AD. *Neurology* **55**, 593-595.

Confaloni A., Terreni L, Piscopo P, Crestini A, Campeggi LM, Frigerio CS, Blotta I, Perri M, Di Natale M, Maletta R, Marcon G, Franceschi M, Bruni AC, Forloni G, Cantafora A (2003): Nicastrin gene in familial and sporadic Alzheimer's disease. *Neuroscience Letters* **353**, 61-65.

Cook LJ, Ho LW, Tazlor AE, Brazne C, Evans JG, Xuereb J, Cairns NJ, Pritchard A, Lemmon H, Mann D, St Clair D, Turic D, Hollingworth P, Moore PJ, Jehu L, Archer N, Walter S, Foy C, Edmondson A, Powel J, Lovestone S, Owen MJ, Williams J, Lendon C, Rubinsztein DC (2004): Candidate gene association studies of the α4 (CHRNA4) and ß2 (CHRNB2) neuronal nicotinic acetylcholine receptor subunit genes in Alzheimer's disease. *Neurosci. Lett.* **358**, 142-146.

Coppede F, Mancuso M, Siciliano G, Migliore L, Murri L (2006): Genes and the environment in neurodegeneration. *Biosci. Rep.* **26**, 341-367.

Corbo RM, Gambina G, Ruggeri M, Scacchi R (2006): Association of estrogen receptor alpha (ESR1) PvuII and XbaI polymorphisms with sporadic Alzheimer's disease and their effect on apolipoprotein E concentrations. *Dement. Geriatr. Cogn. Disord.* **22**, 67-72.

Corder EH, Saunders AM, Risch NJ, Strittmatter WJ, Schmechel DE, Gaskell Jr PC, Rimmler JB, Locke PA, Conneally PM, Schmader KE, Small GW, Roses AD, Haines JL, Pericak-Vance MA (1994): Protective effect of apolipoprotein E type 2 allele for late onset Alzheimer disease. *Nat. Genet.* **7**, 180-184.

Curran M, Middleton D, Edwardson J, Perry R, McKeith I, Morris C, Neill D (1997): HLA-DR antigens associated with major genetic risk for late-onset Alzheimer's disease. *Neuroreport* **8**, 1467-1469.

Desai P, Nebes R, DeKosky ST, Kamboh MI (2005): Investigation of the effect of brain-derived neurotrophic factor (BDNF) polymorphisms on the risk of late-onset Alzheimer's disease (AD) and quantitative measures of AD progression. *Neurosci. Lett.* **379**, 229-234.

Dickson MR, Perry RT, Wiener H, Go RC (2005): Association studies of transforming growth factor-beta 1 and Alzheimer's disease. *Am. J. Med. Genet. B. Neuropsychiatr. Genet.* **139**, 38-41.

Eikelenboom P, Veerhuis R, Scheper W, Rozemuller AJM, van Gool WA, Hoozemans JJM (2006): The significance of neuroinflammation in understanding Alzheimer's disease. *J. Neural. Transm.* **113**, 1685-1695.

Evans DA, Funkenstein HH, Albert MS, Scherr PA, Cook NR, Chown MJ, Hebert LE, Hennekens CH, Taylor JO (1989): Prevalence of Alzheimer's disease in a community population of older persons. Higher than previously reported. *JAMA* **262**, 2551-2556.

Farkas E, De Vos RAI, Jansen Steur ENH, Luiten PGM (2000): Are Alzheimer's disease, hypertension and cerebrocapillary damage related? *Neurobiol. Aging* **21**, 235-243.

Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, Myers RH, Pericak-Vance MA, Risch N, van Duijn CM (1997): Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *J. Am. Med. Assoc.* **278**, 1349-1356.

Farris W, Mansourian S, Chang Y, Lindsley L, Eckman EA, Frosch MP, Eckman CB, Tanzi RE, Selkoe DJ, Guenette S (2003): Insulin-degrading enzyme regulates the levels of insulin, amyloid beta-protein, and the beta-amyloid precursor protein intracellular domain in vivo. *Proc. Natl. Acad. Sci. USA* **100**, 4162-4167.

Ferenčík M, Novák M, Rovensky J, Rybar I (2001): Alzheimer's disease, inflammation and non-steroidal anti-inflammatory drugs. *Bratisl. Lek. Listy.* **102**, 123-132.

Ferri CP, Prince M, Brayne C, Brodaty H, Fratiglioni L, Ganguli M, Hall K, Hasegawa K, Hendrie H, Huang Y, Jorm A, Mathers C, Menezes PR, Rimmer E, Scazufca M (2005): Global prevalence of dementia: a Delphi consensus study. *Lancet* **366**, 2112-2117.

Fidani L, Compton D, Hardy J, Petersen RC, Tangalos E, Mirtsou V, Goulas A, Wavrant De Vrieze F (2002): No association between the lipoprotein lipase S447X polymprphism and Alzheimer's disease. *Neurosci. Lett.* **322**, 192-194.

Fishel MA, Watson GS, Montine TJ, Wang Q, Green PS, Kulstad JJ, Cook DG, Peskind ER, Baker LD, Goldgaber D, Nie W, Asthana S, Plymate SR, Schwartz MW, Craft S (2005): Hyperinsulinemia provokes synchronous increases in central inflammation and beta-amyloid in normal adults. *Arch. Neurol.* **62**, 1539-1544.

Freitag MH, Peila R, Masaki K, Petrovich H, Ross GW, White LR, Launer LJ (2006): Midlife pulse pressure and incidence of dementia – the Honolulu-Asia Aging Study. *Stroke* **37**, 33-37.

Freund-Levi Y, Eriksdotter-Jönhagen M, Cederholm T, Basun, Faxén-Irving G, Garlind A, Vedin I, Vessby B, Wahlund LO, Palmblad J (2006): Omega-3 fatty acid treatment in 174 patients with mild to moderate Alzheimer disease: OmegAD study: a randomized double-blind trial. *Arch. Neurol.* **63**, 1402-1408.

Fung HC, Chen CM, Wu YR, Hsu WC, Ro LS, Lin JC, Chang KH, Wang HK, Lin SJ, Chan H, Lin YY, Wei SL, Hsu Y, Hwang JC, Tung LC, Lee-Chen GJ (2005): Heat shock protein 70 and tumor necrosis factor alpha in Taiwanese patients with dementia. *Dement. Geriatr. Cogn. Disord.* **20**, 1-7.

Gacia M, Safranow K, Styczynska M, Jakubowska K, Peplonska B, Chodakowska-Zebrowska M, Przekop I, Slowik A, Golanska E, Hulas-Bigoszewska K, Chlubek D, Religa D, Zekanowski C, Barcikowska M (2006): Prion protein gene M129 allele is a risk factor for Alzheimer's disease. *J. Neural Transm.* **113**, 1747-1751.

Goddard KA, Olson JM, Payami H, van der Voet M, Kuivaniemi H, Tromp G (2004): Evidence of linkage and association on chromosome 20 for late-onset Alzheimer disease. *Neurogenetics* **5**, 121-128.

Golanska E, Hulas-Bigoszewska K, Rutkiewicz E, Styczynska M, Peplonska B, Barcikowska M, Bratosiewicz-Wasik J, Liberski PP (2004): Polymorphisms within the prion (PrP) and prion-like protein (Doppel) genes in AD. *Neurology* **62**, 313-315.

Gomez-Pinilla F (2007): The influences of diet and exercise on mental health through hormesis. *Aging Res. Rev.* (in press).

Granon S, Faure P, Changeux JP (2003): Executive and social behaviors under nicotinic receptor regulation. Proc. *Natl. Acad. Sci. USA* **100**, 9596-9601.

Grimaldi LM, Casadei VM, Ferri C, Veglia F, Licastro F, Annoni G, Biunno I, De Bellis G, Sorbi S, Mariani C, Canal N, Griffin WS, Franceschi M (2000): Association of early-onset Alzheimer's disease with an interleukin-1alpha gene polymorphism. *Ann. Neurol.* **47**, 361-365.

Grossman H (2003): Does diabetes protect or provoke Alzheimer's disease? Insights into the pathology and future treatment of Alzheimer's disease. *CNS Spectr.* **8**, 815-823.

Grundke-Iqbal I, Iqbal K, Tung YC, Quinlan M, Wisniewski HM, Binder LI (1986): Abnormal phosphorylation of the microtubule-associated protein tau in Alzheimer cytoskeletal pathology. *Proc. Natl. Acad. Sci. USA* **83**, 4913-4917.

Gunstad J, Paul RH, Cohen RA, Tate DF, Gordon E (2006): Obesity is associated with memory deficits in young and middle-aged adults. *Eat. Weight Disord.* **11**, e15-19.

Gunstad J, Paul RH, Cohen RA, Tate DF, Spitznagel MB, Gordon E (2007): Elevated body mass index is associated with executive dysfunction in otherwise healthy adults. *Compr. Psychiatry* **48**, 57-61.

Günther C, von Hadeln K, Müller-Thomsen T, Alberici A, Binetti G, Hock C, Nitsch RM, Stoppe G, Reiss J, Gal A, Finckh U (2004): Possible association of mitochondrial transcription factor A (TFAM) genotype with sporadic Alzheimer disease. *Neurosci. Lett.* **369**, 219-223.

Haag M (2003): Essential fatty acids and the brain. *Can. J. Psychiatry* **48**, 195-203.

Hardy J, Selkoe DJ (2002): The amyloid hypothesis of Alzheimer disease: progress and problems on the road to therapeutics. *Science* **297**, 353-356.

Harris JM, Cumming AM, Craddock N, St Clair D, Lendon CL (2000): Human leucocyte antigen-A2 increases risk of Alzheimer's disease but does not affect age of onset in a Scottish population. *Neurosci. Lett.* **294**, 37-40.

Harrist A, Beech RD, King SL, Zanardi A, Cleary MA, Caldarone BJ, Eisch A, Zoli M, Picciotto MR (2004): Alteration of hippocampal cell proliferation in mice lacking the beta 2 subunit of the neuronal nicotinic acetylcholine receptor. *Synapse* **54**, 200-206.

Hofman A, de Jong PT, van Duijn CM, Breteler MM (2006): Epidemiology of neurological diseases in elderly people: what did we learn from the Rotterdam Study? *Lancet Neurol.* **5**, 545-550.

Hogervorst E, Bandelow S, Combrinck M, Smith AD (2004): Low free testosterone is an independent risk factor for Alzheimer's disease. *Exp. Gerontol.* **39**, 1633-1639.

Inzitari M, Pozzi C, Rinaldi LA, Masotti G, Marchionni N, Di Bari M (2007): Cognitive and functional impairment in hypertensive brain microangiopathy. *J. Neurol. Sci.* **257**, 166-173.

Ishunina TA, Swaab DF (2001): Increased expression of estrogen receptor alpha and beta in the nucleus basalis of Meynert in Alzheimer's disease. *Neurobiol. Aging* **22**, 417-426.

Itzhaki RF, Lin WR, Shang D, Wilcock GK, Faragher B, Jamieson GA (1997): Herpes simplex virus type 1 in brain and risk of Alzheimer's disease. *Lancet* **349**, 241-244.

Jelinger KA, Paulus W, Wrocklage C, Litvan I (2001): Traumatic brain injury as a risk factor for Alzheimer disease. Comparison of two retrospective autopsy cohorts with evaluation of ApoE genotype. *BMC Neurology* **1**, 3.

Kamboh MI (2004): Molecular genetics of late-onset Alzheimer's disease. *Ann. Hum. Genet.* **68**, 381-404.

Kamboh MI, Minster RL, Feingold E, DeKosky ST (2006): Genetic association of ubiquilin with Alzheimer's disease and related quantitative measures. *Mol. Psychiatry* **11**, 273-279.

Katzov H, Chalmers K, Palmgren J, Andreasen N, Johansson B, Cairns NJ, Gatz M, Wilcock GK, Love S, Pedersen NL, Brookes AJ, Blennow K, Kehoe PG, Prince JA (2004): Genetic variants of ABCA1 modify Alzheimer disease risk and quantitative traits related to beta-amyloid metabolism. *Hum. Mutat.* **23**, 358-367.

Kehoe PG, Russ C, McIlory S, Williams H, Holmans P, Holmes C, Liolitsa D, Vahidassr D, Powell J, McGleenon B, Liddell M, Plomin R, Dynan K, Williams N, Neal J, Cairns NJ, Wilcock G, Passmore P, Lovestone S, Williams J, Owen MJ (1999): Variation in DCP1, encoding ACE, is associated with susceptibility to Alzheimer disease. *Nat. Genet*. **21**, 71-72.

Kehoe PG, Katzov H, Feuk L, Bennet AM, Johansson B, Wiman B, de Faire U, Cairns NJ, Wilcock GK, Brookes AJ, Blennow K, Prince JA (2003): Haplotypes extending across ACE are associated with Alzheimer's disease. *Hum. Mol. Genet.* **12**, 859-867.

Ki CS, Na DL, Kim DK, Kim HJ, Kim JW (2002): Genetic association of an apolipoprotein C-I (APOC1) gene polymorphism with late-onset Alzheimer's disease. *Neurosci. Lett.* **319**, 75-78.

Kivipelto M, Helkala EL, Laakso MP, Hanninen T, Hallikainen M, Alhainen K, Soininnen H, Tuomilehto J, Nissien A (2001): Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ* **322**, 1447-1451.

Kramer AF, Erickson KI (2007): Capitalizing on cortical plasticity: influence of physical activity on cognition and brain function. *Trends Cogn. Sci.* **11**, 342-348.

Kramer AF, Hahn S, Cohen NJ, Banich MT, McAuley E, Harrison CR, Chason J, Vakil E, Bardell L, Boileau RA, Colcombe A (1999): Ageing, fitness and neurocognitive function. *Nature* **400**, 418-419.

Kravitz HM, Meyer PM, Seeman TE, Greendale GA, Sowers MR (2006): Cognitive functioning and sex steroid hormone

gene polymorphisms in women at midlife. *Am. J. Med.* **119**, S94-S102.

Kunugi H, Ueki A, Otsuka M, Isse K, Hirasawa H, Kato N, Nabika T, Kobayashi S, Nanko S (2001): A novel polymorphism of the brain-derived neurotrophic factor (BDNF) gene associated with late-onset Alzheimer's disease. *Mol. Psychiatry* **6**, 83-86.

Kuwano R, Miyashita A, Arai H, Asada T, Imagawa M, Shoji M, Higuchi S, Urakami K, Kakita A, Takahashi H, Tsukie T, Toyabe S, Akazawa K, Kanazawa I, Ihara Y (2006): Dynamin-binding protein gene on chromosome 10q is associated with late-onset Alzheimer's disease. *Hum. Mol. Genet.* **15**, 2170-2182.

Lambeth JD (2007): Nox enzymes, ROS, and chronic disease: an example of antagonistic pleiotropy. *Free Radic. Biol. Med.* **43**, 332-347.

Landen M, Thorsell A, Wallin A, Blennow K (1996): The apolipoprotein E allele epsilon 4 does not correlate with the number of senile plaques or neurofibrillary tangles in patients with Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry* **61**, 352-356.

Larson EB, Wang L, Bowen JD, McCormick WC, Teri L, Crane P, Kukull W (2006): Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. *Ann. Intern. Med.* **144**, 73-81.

Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K (2001): Physical activity and risk of cognitive impairment and dementia in elderly persons. *Arch. Neurol.* **58**, 498-504.

Lazarov O, Robinson J, Tang YP, Hairston IS, Korade-Mirnics Z, Lee VM, Hersh LB, Sapolsky RM, Mirnics K, Sisodia SS (2005): Environmental enrichment reduces Abeta levels and amyloid deposition in transgenic mice. *Cell* **120**, 701-713.

Lehmann DJ, Barnardo MC, Fuggle S, Quiroga I, Sutherland A, Warden DR, Barnetson L, Horton R, Beck S, Smith AD (2006): Replication of the association of HLA-B7 with Alzheimer's disease: a role for homozygosity? *J. Neuroinflammation* **3**, 1-7.

Levi O, Jongen-Relo AL, Feldon J, Roses AD, Michaelson DM (2003): ApoE4 impairs hippocampal plasticity isoform-specifically and blocks the environmental stimulation of synaptogenesis and memory. *Neurobiol. Dis.* **13**, 273-282.

Levin ED, McClernon FJ, Rezvani AH (2006): Nicotinic effects on cognitive function: behavioral characterization, pharmacological specification, and anatomic localization. *Psychopharmacology* **184**, 523-539.

Li X, Rowland LP, Mitsumoto H, Przedborski S, Bird TD, Schellenberg GD, Peskind E, Johnson N, Siddique T, Mesulam MM, Weintraub S, Mastrianni JA (2005): Prion protein codon 129 genotype prevalence is altered in primary progressive aphasia. *Ann. Neurol.* **58**, 858-864.

Li Y, Liu L, Barger SW, Griffin WST (2003): Interleukin-1 Mediates Pathological Effects of Microglia on Tau Phosphorylation and on Synaptophysin Synthesis in Cortical Neurons through a p38-MAPK Pathway. *J. Neurosci.* **23**, 1605-1611.

Li Y, Chu LW, Chen YQ, Cheung BM, Leung RY, Yik PY, Ng KM, Mak W, Jin DY, St George-Hyslop P, Song YQ. (2006): Intron 2 (T/C) CYP46 polymorphism is associated with Alzheimer's disease in Chinese patients. *Dement. Geriatr. Cogn. Disord.* **22**, 399-404.

Licastro F, Chiappelli M (2003): Brain immune responses cognitive decline and dementia: relationship with phenotype expression and genetic background. *Mech. Ageing Dev.* **124**, 539-548.

Licastro F, Grimaldi LM, Bonafe M, Martina C, Olivieri F, Cavallone L, Giovanietti S, Masliah E, Franceschi C (2003): Interleukin-6 gene alleles affect the risk of Alzheimer's disease and levels of the cytokine in blood and brain. *Neurobiol. Aging* **24**, 921-926.

Lin WR, Wozniak MA, Cooper RJ, Wilcock GK, Itzhaki RF (2002): Herpesviruses in brain and Alzheimer's disease. *J. Pathol.* **197**, 395-402.

Lio D, Annoni G, Licastro F, Crivello A, Forte GI, Scola L, Colonna-Romano G, Candore G, Arosio B, Galimberti L, Vergani C, Caruso C (2006a): Tumor necrosis factor-alpha 308A/G polymorphism is associated with age at onset of Alzheimer's disease. *Mech. Ageing Dev.* **127**, 567-571.

Lio D, Scola L, Crivello A (2006b): Immunogenic markers and the sporadic Alzheimer's disease diagnostic knot. *ASHI Quarterly* Fourth Quarter 2006, 104-106.

Luckhaus C, Sand PG (2007): Estrogen Receptor 1 gene (ESR1) variants in Alzheimer's disease. Results of a meta-analysis. *Aging Clin. Exp. Res.* **19**, 165-168.

Luchsinger JA, Reitz C, Patel B, Tang MX, Manly JJ, Mayeux R (2007a): Relation of diabetes to mild cognitive impairment. *Arch. Neurol.* **64**, 570-575.

Luchsinger JA, Tang MX, Miller J, Green, Mayeux R (2007b): Relation of higher folate intake to lower risk of Alzheimer disease in the elderly. *Arch. Neurol.* **64**, 86-92.

Luedecking EK, DeKosky ST, Mehdi H, Ganguli M, Kamboh MI (2000): Analysis of genetic polymorphisms in the transforming growth factor-beta1 gene and the risk of Alzheimer's disease. *Hum. Genet.* **106**, 565-569.

Lupien SJ, de Leon M, de Santi S, Convit A, Tarshish C, Nair NP, Thakur M, McEwen BS, Hauger RL, Meaney MJ (1998): Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nat. Neurosci.* **1**, 69-73.

Lye TC, Shores A (2000): Traumatic injury as a risk factor for Alzheimer's disease: A review. *Neuropsychol. Rev.* **10**, 115-129.

Ma SL, Tang NL, Lam LC, Chiu HF (2006): Polymorphisms of the cholesterol 24-hydroxylase (CYP46A1) gene and the risk of Alzheimer's disease in a Chinese population. *Int. Psychogeriatr.* **18**, 37-45.

Martin-Rehrmann MD, Cho HS, Rebeck GW. (2002): Lack of association of two lipoprotein lipase polymorphisms with Alzheimer's disease. *Neurosci. Lett.* **328**, 109-112.

Masters CL, Beyreuther K (2006): Pathways to the discovery of the Abeta amyloid of Alzheimer's disease. *J. Alzheimers Dis.* **9** (3 Suppl.) 155-161.

Matsushita S, Arai H, Matsui T, Yuzuriha T, Urakami K, Masaki T, Higuchi S (2005): Brain-derived neurotrophic factor

gene polymorphisms and Alzheimer's disease. *J. Neural. Transm.* **112**, 703-711.

McGeer PL, Itagaki S, Tago H, McGeer EG (1987): Reactive microglia in patients with senile dementia of Alzheimer-type are positive for the histocompatibility glycoprotein HLA-DR. *Neurosci. Lett.* **79**, 195-200.

McGeer PL, McGeer EG (2007): NSAIDs and Alzheimer disease: epidemiological, animal model and clinical studies. *Neurobiol. Aging* **28**, 639-647.

Minster RL, Dekosky ST, Kamboh MI (2007): No association of dynamin binding protein (DNMBP) gene SNPs and Alzheimer's disease. *Neurobiol. Aging* (in press).

Monastero R, Camarda C, Cefalu AB, Caldarella R, Camarda LK, Noto D, Averna MR, Camarda R (2005): No association between the cystatin C gene polymorphism and Alzheimer's disease: a case-control study in an Italian population. *J. Alzheimers Dis.* **7**, 291-295.

Mortimer JA, Borenstein AR, Gosche KM, Snowdon DA (2005): Very early detection of Alzheimer neuropathology and the role of brain reserve in modifying its clinical expression. *J. Geriatr. Psychiatry Neurol.* **18**, 218-223.

Mukherjee O, Kauwe JS, Mayo K, Morris JC, Goate AM (2007): Haplotype-based association analysis of the MAPT locus in late onset Alzheimer's disease. *BMC Genet.* **8**, 3.

Myers AJ, Kaleem M, Marlowe L, Pittman AM, Lees AJ, Fung HC, Duckworth J, Leung D, Gibson A, Morris CM, de Silva R, Hardy J (2005): The H1c haplotype at the MAPT locus is associated with Alzheimer's disease. *Hum. Mol. Genet.* **14**, 2399-2404.

Nagy Z, Esiri MM, Jobst KA, Johnston C, Litchfield S, Sim E, Smith AD (1995): Influence of the apolipoprotein E genotype on amyloid deposition and neurofibrillary tangle formation in Alzheimer's disease. *Neuroscience* **69**, 757-761.

Narain Y, Yip A, Murphy T, Brayne C, Easton D, Evans JG, Xuereb J, Cairns N, Esiri MM, Furlong RA, Rubinsztein DC (2000): The ACE gene and Alzheimer's disease susceptibility. *J. Med. Genet.* **37**, 695-697.

Novák M, Jakes R, Edwards PC, Milstein C, Wischik CM (1991): Difference between the tau protein of Alzheimer paired helical filament core and normal tau revealed by epitope analysis of monoclonal antibodies 423 and 7.51. *Proc. Natl. Acad. Sci. USA* **88**, 5837-5841.

Novák M, Kabát J, Wischik CM (1993): Molecular characterization of the minimal protease resistant tau unit of the Alzheimer's disease paired helical filament. *EMBO J.* **12**, 365-370.

Ohkubo T, Sakasegawa Y, Asada T, Kinoshita T, Goto Y, Kimura H, Mizusawa H, Hachiya NS, Kaneko K (2003): Absence of association between codon 129/219 polymorphisms of the prion protein gene and Alzheimer's disease in Japan. *Ann. Neurol.* **54**, 553-554.

Olsen L, Rasmussen HB, Hansen T, Bagger YZ, Tanko LB, Qin G, Christiansen C, Werge T (2006): Estrogen receptor alpha and risk for cognitive impairment in postmenopausal women. *Psychiatr. Genet.* **16**, 85-88.

Orlacchio A, Kawarai T, Polidoro M, Stefani A, Orlacchio A, St George-Hyslop PH, Bernardi G (2002): Association analysis between Alzheimer's disease and the Nicastrin gene polymorphisms. *Neurosci. Lett.* **333**, 115–118.

Ott A, Slooter AJ, Hofman A, van Harskamp F, Witteman JC, Van Broeckhoven C, van Duijn CM, Breteler MM (1998): Smoking and risk of dementia and Alzheimer's disease in a population-based cohort study: the Rotterdam Study. *Lancet* **351**, 1840-1843.

Papassotiropoulos A, Lambert JC, Wavrant-De Vrieze F, Wollmer MA, von der Kammer H, Streffer JR, Maddalena A, Huynh KD, Wolleb S, Lutjohann D, Schneider B, Thal DR, Grimaldi LM, Tsolaki M, Kapaki E, Ravid R, Konietzko U, Hegi T, Pasch T, Jung H, Braak H, Amouyel P, Rogaev EI, Hardy J, Hock C, Nitsch RM (2005): Cholesterol 25-hydroxylase on chromosome 10q is a susceptibility gene for sporadic Alzheimer's disease. *Neurodegener. Dis.* **2**, 233-241.

Peavy GM, Lange KL, Salmon DP, Patterson TL, Goldman S, Gamst AC, Mills PJ, Khandrika S, Galasko D (2007): The effects of prolonged stress and APOE genotype on memory and cortisol in older adults. *Biol. Psychiatry* **62**, 472-478.

Petrovitch H, White LR, Izmirilian G, Ross GW, Havlik RJ, Markesbery W, Nelson J, Davis DG, Hardman J, Foley DJ, Launer LJ (2000): Midlife blood pressure and neuritic plaques, neurofibrillary tangles, and brain weight at death: the HAAS. *Neurobiol. Aging* **21**, 57-62.

Potter H, Wefes IM, Nilsson LN (2001): The inflammation-induced pathological chaperones ACT and apo-E are necessary catalysts of Alzheimer amyloid formation. *Neurobiol. Aging* **22**, 923-930.

Prince JA, Feuk L, Sawyer SL, Gottfries J, Ricksten A, Nägga K, Bogdanovic N, Blennow K, Brookes AJ (2001): Lack of replication of association findings in complex disease: an analysis of 15 polymorphisms in prior candidate genes for sporadic Alzheimer's disease. *Eur. J. Hum. Genet.* **9**, 437-444.

Qiu C, De Ronchi D, Fratiglioni L (2007): The epidemiology of the dementias: an update. *Curr. Opin. Psychiatry* **20**, 380-385.

Quadri P, Fragiacomo C, Pezzati R, Zanda E, Forloni G, Tettamanti M, Lucca U (2004): Homocysteine, folate, and vitamin B-12 in mild cognitive impairment, Alzheimer disease, and vascular dementia. *Am. J. Clin. Nutr.* **80**, 114-122.

Ramos EM, Lin MT, Larson EB, Maezawa I, Tseng LH, Edwards KL, Schellenberg GD, Hansen JA, Kukull WA, Jin LW (2006): Tumor necrosis factor alpha and interleukin 10 promoter region polymorphisms and risk of late-onset Alzheimer disease. *Arch. Neurol.* **63**, 1165-9116.

Rapp SR, Espeland MA, Shumaker SA, Henderson VW, Brunner RL, Manson JE, Gass ML, Stefanick ML, Lane DS, Hays J, Johnson KC, Coker LH, Dailey M, Bowen D (2003): Effect of estrogen plus progestin on global cognitive function in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA* **289**, 2663-2672.

Ravaglia G, Forti P, Maioli F, Martelli M, Servadei L, Brunetti N, Porcellini E, Licastro F (2005): Homocysteine and folate as risk factors for dementia and Alzheimer disease. *Am. J. Clin. Nutr.* **82**, 636-643.

Reed T, Carmelli D, Swan GE, Breitner JCS, Welsh K, Jarvik GP, Deeb S, Auwerx J. (1994): Lower cognitive performance in normal older adult male twins carrying the apolipoprotein E epsilon 4 allele. *Arch. Neurol.* **51**, 1189-1192

Refolo LM, Pappolla MA, Malester B, LaFrancois J, Bryant-Thomas T, Wang R, Tint GS, Sambamurti K, Duff K (2000): Hypercholesterolemia accelerates the Alzheimer's amyloid pathology in a transgenic mouse model. *Neurobiol. Dis.* **7**, 321-331.

Retz W, Thome J, Durany N, Harsanyi A, Retz-Junginger P, Kornhuber J, Riederer P, Rosler M (2001): Potential genetic markers of sporadic Alzheimer's dementia. *Psychiatr. Genet.* **11**, 115-122.

Richard F, Fromentin-David I, Ricolfi F, Ducimetičre P, Di Menza C, Amouyel P, Helbecque N (2001): The angiotensin I converting enzyme gene as a susceptibility factor for dementia. *Neurology* **56**, 1593-1595.

Riemenschneider M, Schwarz S, Wagenpfeil S, Diehl J, Müller U, Förstl H, Kurz A (2002): A polymorphism of the brain-derived neurotrophic factor (BDNF) is associated with Alzheimer's disease in patients lacking the Apolipoprotein E epsilon4 allele. *Mol. Psychiatry* **7**, 782-785.

Riemenschneider M, Mahmoodzadeh S, Eisele T, Klopp N, Schwarz S, Wagenpfeil S, Diehl J, Mueller U, Foerstl H, Illig T, Kurz A (2004): Association analysis of genes involved in cholesterol metabolism located within the linkage region on chromosome 10 and Alzheimer's disease. *Neurobiol. Aging* **25**, 1305-1308.

Rockwood K, Kirkland S, Hogan DB, MacKnight C, Merry H, Verreault R, Wolfson C, McDowell I (2002): Use of lipid-lowering agents, indication bias, and the risk of dementia in community-dwelling elderly people. *Arch. Neurol.* **59**, 223-227.

Rogaeva E, Meng Y, Lee JH, Gu Y, Kawarai T, Zou F, Katayama T, Baldwin CT, Cheng R, Hasegawa H, Chen F, Shibata N, Lunetta KL, Pardossi-Piquard R, Bohm C, Wakutani Y, Cupples LA, Cuenco KT, Green RC, Pinessi L, Rainero I, Sorbi S, Bruni A, Duara R, Friedland RP, Inzelberg R, Hampe W, Bujo H, Song YQ, Andersen OM, Willnow TE, Graff-Radford N, Petersen RC, Dickson D, Der SD, Fraser PE, Schmitt-Ulms G, Younkin S, Mayeux R, Farrer LA, St George-Hyslop P (2007): The neuronal sortilin-related receptor SORL1 is genetically associated with Alzheimer disease. *Nat. Genet.* **39**, 168-177.

Roman GC, Kalaria RN (2006): Vascular determinants of cholinergic deficits in Alzheimer disease and vascular dementia. *Neurobiol. Aging* **27**, 1769-1785.

Russ C, Powel JF, Zhao J, Baker M, Hutton M, Crawford F, Mullan M, Roks G, Cruts M, Lovestone S (2001): The microtubule associated protein tau gene and Alzheimer's disease – an association study and meta-analysis. *Neurosci. Lett.* **314**, 92-96.

Sabbatini M, Tomassoni D, Amenta F (2001): Hypertensive brain damage: comparative evaluation of protective effect of treatment with dihydropyridine derivatives in spontaneously hypertensive rats. *Mech. Ageing Develop.* **122**, 2085-2105.

Salerno-Kennedy R, Cashman KD (2005): Relationship between dementia and nutrition-related factors and disorders: an overview. *Int. J. Vitam. Nutr. Res.* **75**, 83-95.

Saugstad LF (2006): Are neurodegenerative disorder and psychotic manifestations avoidable brain dysfunctions with adequate dietary omega-3? *Nutr. Health* **18**, 89-101.

Scacchi R, Gambina G, Broggio E, Moretto G, Ruggeri M, Corbo RM (2004): The H+ allele of the lipoprotein lipase (LPL) HindIII intronic polymorphism and the risk for sporadic late-onset Alzheimer's disease. *Neurosci. Lett.* **367**, 177–180.

Schmidt R, Schmidt H, Curb JD, Masaki K, White LR, Launer LJ (2002): Early inflammation and dementia: a 25-year follow-up of the Honolulu-Asia Aging Study. *Ann. Neurol.* **52**, 168-174.

Selkoe DJ (2001): Alzheimer's disease: genes, proteins, and therapy. *Physiol. Rev.* **81**, 741-766.

Seripa D, Forno GD, Matera MG, Gravina C, Margaglione M, Palermo MT, Wekstein DR, Antuono P, Davis DG, Daniele A, Masullo C, Bizzarro A, Gennarelli M, Fazio VM (2003): Methylenetetrahydrofolate reductase and angiotensin converting enzyme gene polymorphisms in two genetically and diagnostically distinct cohort of Alzheimer patients. *Neurobiol. Aging* **24**, 933-939.

Seshadri S, Zornberg GL, Derby LE, Myers MW, Jick H, Drachman DA (2001): Postmenopausal estrogen replacement therapy and the risk of Alzheimer disease. *Arch. Neurol.* **58**, 435-440.

Seshadri S (2006): Elevated plasma homocysteine levels: risk factor or risk marker for the development of dementia and Alzheimer's disease? *J. Alzheimers Dis.* **9**, 393-398.

Shibata N, Kawarai T, Lee JH, Lee HS, Shibata E, Sato C, Liang Y, Duara R, Mayeux RP, St George-Hyslop PH, Rogaeva E. (2006): Association studies of cholesterol metabolism genes (CH25H, ABCA1 and CH24H) in Alzheimer's disease. *Neurosci. Lett.* **391**,142-146.

Slifer MA, Martin ER, Bronson PG, Browning-Large C, Doraiswamy PM, Welsh-Bohmer KA, Gilbert JR, Haines JL, Pericak-Vance MA (2006): Lack of association between UBQLN1 and Alzheimer disease. *Am. J. Med. Genet. B. Neuropsychiatr. Genet.* **141**, 208-213.

Small GW, Scott WK, Komo S, Yamaoka LH, Farrer LA, Auerbach SH, Saunders AM, Roses AD, Haines JL, Pericak-Vance MA (1999): No association between the HLA-A2 allele and Alzheimer disease. *Neurogenetics* **2**, 177-182.

Smemo S, Nowotny P, Hinrichs AL, Kauwe JS, Cherny S, Erickson K, Myers AJ, Kaleem M, Marlowe L, Gibson AM, Hollingworth P, O'Donovan MC, Morris CM, Holmans P, Lovestone S, Morris JC, Thal L, Li Y, Grupe A, Hardy J, Owen MJ, Williams J, Goate A (2006): Ubiquilin 1 polymorphisms are not associated with late-onset Alzheimer's disease. *Ann. Neurol.* **59**, 21-26.

Sparks LD, Scheff SW, Liu H, Landers TM, Coyne CM, Hunsaker III JC (1995): Increased incidence of neurofibrillary tangles (NFT) in non-demented individuals with hypertension. *J. Neurol. Sci.* **131**, 162-169.

Stellwagen D, Malenka RC (2006): Synaptic scaling mediated by glial TNF-alpha. *Nature* **440**, 1054-1059.

Stern Y (2006): Cognitive reserve and Alzheimer disease. *Alzheimer Dis. Assoc. Disord.* **20**, 112-117.

Strandberg TE, Pitkala KH, Linnavuori K, Tilvis RS (2004): Cognitive impairment and infectious burden in the elderly. *Arch. Gerontol. Geriatr.* **9**, (Suppl.) 419-423.

Suh YH, Checler F (2002): Amyloid precursor protein, presenilins and α-synuclein: molecular pathogenesis and pharmacological applications in Alzheimer's disease. *Pharmacol. Rev.* **54**, 469-525.

Szczygielski J, Mautes A, Steudel WI, Falkai P, Bayer TA, Wirths O (2005): Traumatic brain injury: cause or risk of Alzheimer's disease? A review of experimental studies. *J. Neural Transm.* **112**, 1547-1564.

Tan ZS, Beiser AS, Vasan RS, Roubenoff R, Dinarello CA, Harris TB, Benjamin EJ, Au R, Kiel DP, Wolf PA, Seshadri S (2007): Inflammatory markers and the risk of Alzheimer disease: the Framingham Study. *Neurology* **68**, 1902-1908.

Tannenberg RK, Scott HL, Tannenberg AE, Dodd PR (2006): Selective loss of synaptic proteins in Alzheimer's disease: evidence for an increased severity with APOE var epsilon4. *Neurochem. Int.* **49**, 631-639.

Tarkowski E, Liljeroth AM, Nilsson A, Ricksten A, Davidsson P, Minthon L, Blennow K (2000): TNF gene polymorphism and its relation to intracerebral production of TNFalpha and TNFbeta in AD. *Neurology* **54**, 2077-2081.

Taubes G (2003): Neuroscience. Insulin insults may spur Alzheimer's disease. *Science* **301**, 40-41.

Tuppo EE, Arias HR (2005): The role of inflammation in Alzheimer's disease. *Int. J. Biochem. Cell. Biol.* **37**, 289-305.

Tycko B, Lee JH, Ciappa A, Saxena A, Li CM, Feng L, Arriaga A, Stern Y, Lantigua R, Shachter N, Mayeux R (2004): APOE and APOC1 promoter polymorphisms and the risk of Alzheimer disease in African American and Caribbean Hispanic individuals. *Arch. Neurol.* **61**, 1434-1439.

van Oijen M, Witteman JC, Hofman A, Koudstaal PJ, Breteler MM (2005): Fibrinogen is associated with an increased risk of Alzheimer disease and vascular dementia. *Stroke* **36**, 2637-2641.

van Oijen M, Arp PP, de Jong FJ, Hofman A, Koudstaal PJ, Uitterlinden AG, Breteler MM (2006): Polymorphisms in the interleukin 6 and transforming growth factor beta1 gene and risk of dementia. The Rotterdam Study. *Neurosci. Lett.* **402**, 113-117.

Venters HD, Dantzer R, Kelley KW (2000): Tumor necrosis factor-alpha induces neuronal death by silencing survival signals generated by the type I insulin-like growth factor receptor. *Ann. N.Y. Acad. Sci.* **917**, 210-220.

Verreault R, Laurin D, Lindsay J, De Serres G (2001): Past exposure to vaccines and subsequent risk of Alzheimer's disease. *CMAJ* **165**, 1495–1498.

Wang L, Larson EB, Bowen JD, van Belle G (2006): Performance-based physical function and future dementia in older people. *Arch. Intern. Med.* **166**, 1115-1120.

Wang F, Jia J (2007): Polymorphisms of cholesterol metabolism genes CYP46 and ABCA1 and the risk of sporadic Alzheimer's disease in Chinese. *Brain Res.* **1147**, 34-38.

Watson GS, Craft S (2003): The role of insulin resistance in the pathogenesis of Alzheimer's disease: implications for treatment. *CNS drugs* **17**, 27-45.

Watson GS, Bernhardt T, Reger MA, Cholerton BA, Baker LD, Peskind ER, Asthana S, Plymate SR, Frolich L, Craft S (2006): Insulin effects on CSF norepinephrine and cognition in Alzheimer's disease. *Neurobiol. Aging* **27**, 38-41.

Webber KM, Casadesus G, Perry G, Atwood CS, Bowen R, Smith MA (2005): Gender differences in Alzheimer's disease: the role of luteinizing hormone in disease pathogenesis. *Alzheimer. Dis. Assoc. Disord.* **19**, 95-99.

Whitmer RA, Gunderson EP, Barrett-Connor E, Quesenberry Jr CP, Yaffe K (2005): Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. *BMJ* **330**, 1360.

Wilson RS, Arnold SE, Schneider JA, Kelly JF, Tang Y, Bennett DA (2006): Chronic psychological distress and risk of Alzheimer's disease in old age. *Neuroepidemiology* **27**, 143-153.

Wilson RS, Krueger KR, Arnold SE, Schneider JA, Kelly JF, Barnes LL, Tang Y, Bennett DA (2007): Loneliness and risk of Alzheimer disease. *Arch. Gen. Psychiatry* **64**, 234-240.

Wischik CM, Novák M, Thøgersen HC, Edwards PC, Runswick MJ, Jakes R, Walker JE, Milstein C, Roth M, Klug A (1988): Isolation of a fragment of tau derived from the core of paired helical filament of Alzheimer's disease, *Proc. Natl. Acad. Sci. USA* **85**, 4506-4510.

Wolozin B, Kellman W, Ruosseau P, Celesia GG, Siegel G (2000): Decreased Prevalence of Alzheimer Disease Associated With 3-Hydroxy-3-Methyglutaryl Coenzyme A Reductase Inhibitors. *Arch. Neurol.* **57**, 1439-1443.

Zandi PP, Breitner JC (2001): Do NSAIDs prevent Alzheimer's disease? And, if so, why? The epidemiological evidence. *Neurobiol. Aging* **22**, 811-817.

Zhou B, Teramukai S, Fukushima M (2007): Prevention and treatment of dementia or Alzheimer's disease by statins: a meta-analysis. *Dement. Geriatr. Cogn. Disord.* **23**,194-201.

Žilka N, Ferenčík M, Hulín I (2006): Neuroinflammation in Alzheimer's disease: protector or promoter? *Bratisl. Med. J.* **107**, 374-383.

Zonderman AB (2005): Predicting Alzheimer's disease in the Baltimore Longitudinal Study of Aging. *J. Geriatr. Psychiatry Neurol.* **18**, 192-195.