

Inflammation in Neurodegenerative Disorders: Friend or Foe?

Daniela Galimberti*, Chiara Fenoglio and Elio Scarpini

Dept. of Neurological Sciences, "Dino Ferrari" Center, University of Milan, Fondazione Ospedale Maggiore Policlinico IRCCS, Via F. Sforza 35, 20122, Milan, Italy

Abstract: Inflammation plays a role in the development of Alzheimer's disease (AD). Several cytokines and chemokines have been detected both immunohistochemically and in cerebrospinal fluid from patients. Some of them, including Tumor Necrosis Factor- α , Interferon- γ -inducible Protein-10, Monocyte Chemoattractant Protein-1 and Interleukin-8, are increased in AD and in Mild Cognitive Impairment (MCI), considered the prodromal stage of AD, suggesting that these modifications occur very early during the development of the disease, possibly explaining the failure of trials with anti-inflammatory agents in patients with severe AD. Further evidence suggests that cytokines and chemokines could have a role in other neurodegenerative disorders, such as Frontotemporal Lobar Degeneration and Amyotrophic Lateral Sclerosis. In this regard, analogies and differences among these neurodegenerative disorders will be discussed.

Neurodegenerative disorders are considered multifactorial diseases, and genetic factors influence pathological events and contribute to change the disease phenotype from patient to patient. Gene polymorphisms in crucial molecules, including cytokines, chemokines and molecules related to oxidative stress, may act as susceptibility factors, increasing the risk of disease development, or may operate as regulatory factors, modulating the severity of pathogenic processes or the response to drug treatment. With these premises, genetic studies recently carried out will be described and discussed in detail.

Keywords: Alzheimer's disease (AD), frontotemporal lobar degeneration (FTLD), amyotrophic lateral sclerosis (ALS), inflammation, cytokines, chemokines.

1. INFLAMMATION AND ALZHEIMER'S DISEASE

1.1. Clinical and Neuropathological Features

Alzheimer's disease (AD) is the most common cause of dementia in the elderly, with a prevalence of 5% after 65 years of age, increasing to about 30% in people aged 85 years or older. Originally described by Alois Alzheimer and Gaetano Perusini in 1906, it is clinically characterized by a progressive cognitive impairment, including impaired judgement, decision-making and orientation, often accompanied, in later stages, by psychobehavioral disturbances as well as language impairment (Table 1). Mutations in genes encoding for β -amyloid precursors protein or presenilin 1 and presenilin 2 genes (β -APP, *PSEN1* and *PSEN2*, respectively, Table 2) account for about 5-10% of cases, characterized by an early onset (before 65 years). So far, 26 different mutations, causing amino acid changes in putative sites for the cleavage of the protein, have been described in the APP gene in 72 families, together with 156 mutations in *PSEN1* in 342 families and 10 mutations in *PSEN2* in 16 families (<http://molgen-www.ua.ac.be>).

The two major neuropathological hallmarks of AD are extracellular beta-amyloid (A β) plaques and intracellular neurofibrillary tangles (NFTs). The production of A β , which represents a crucial step in AD pathogenesis, is the result of cleavage of A β precursor protein (β -APP) that is overexpressed in AD [1]. A β forms highly insoluble and proteolysis resistant fibrils known as senile plaques (SP). In contrast to

the low-fibrillar A β plaques (diffuse plaques), highly fibrillar (amyloidogenic) forms of A β plaques are associated with glial and neuritic changes of the surrounding tissue (neuritic-plaques) [2]. β -APP displays important developmental functions in cell differentiation, and possibly in the establishment of synapses [3]. Its function in the adult brain is less clear, although it seems to be associated with neuronal growth and survival [1]. It is in fact expressed by neurons in response to cell injury; i.e. β -APP is a marker for axonal damage after a head injury [4] and its levels are markedly increased in affected areas of the brain in temporal lobe epilepsy [5].

NFTs are composed of the tau protein. In healthy controls, tau is a component of microtubules, which represent the internal support structures for the transport of nutrients, vesicles, mitochondria and chromosomes within the cell. Microtubules also stabilize growing axons, which are necessary for the development and growth of neurites [1]. In AD, tau protein is abnormally hyperphosphorylated and forms insoluble fibrils, which originate deposits within the cell.

Neurodegeneration in AD is estimated to start 20-30 years before clinical onset. During this preclinical phase, plaque and tangle load increases, and at a certain threshold the first symptoms appear. This clinical phase is designed as mild cognitive impairment (MCI) [6] and is an etiologically heterogeneous entity. In fact, many subjects with MCI have prodromal AD, whereas others have a benign form of MCI as part of the normal ageing process and some have other disorders such as vascular dementia [7]. Recent data show that subjects with amnesic MCI display the early neuropathological changes of AD, and thus, in reality, represent early AD [8].

*Address correspondence to this author at the Department of Neurological Sciences, "Dino Ferrari" Center, University of Milan, Fondazione Ospedale Maggiore Policlinico IRCCS, Via F. Sforza 35, 20122, Milan, Italy; Tel: ++39.2.55033858; Fax: ++39.2.50320430; E-mail: daniela.galimberti@unimi.it

Table 1. Characteristics of AD and FTL

	AD	FTLD
History	Increases with age, Memory > behavior, Indifference	Presenile, Behavior > memory, Disinhibition
Pathology	Senile plaques, Neurofibrillary tangles, Neuronal loss, Microglial activation	-Frontal lobe degeneration type: microvacuolation, gliosis, neuron loss; without Pick bodies -Pick-type: Pick bodies, inflated cells, intense astrocytosis -Motor neuron disease type
Mental Status Examination	Minor executive dysfunction, Amnesia, Visuospatial dysfunction, Acalculia	Major executive dysfunction, Retrieval deficit, Visuospatial skills preserved, Calculation preserved
Neuropsychological Assessment	More severe memory loss, Memory performance worse than executive function	Calculations, constructions better preserved, Executive performance worse than memory
Language	Anomia early (lexical selection type), Transcortical sensory aphasia	Semantic aphasia, Progressive nonfluent aphasia
Neuropsychiatric Features	Psychosis in 50%, Disinhibition mild Euphoria rare, Stereotyped behaviors rare	Psychosis in 25%, Disinhibition severe, Euphoria in 1/3, Stereotyped behaviors common

Table 2. Main Causative Genes of FAD and Genes Claimed to be Potential Susceptibility or Modifier Factors for SAD

Gene	Chromosome	Association	Reference
APP	21q21	Familial	[140]
PSEN1	14q24.3	Familial	[141]
PSEN2	1q31-q42	Familial	[142]
APOE	19q13.32	Sporadic	[89]
IL1- α	2q14-q21	Sporadic	[96]
IL1- β	2q14-q21	Sporadic	[97]
IL-1R	2q14-q21	Sporadic	[95]
IL-6	7p21	Sporadic	[96]
TNF- α	6p21.3	Sporadic	[100]
ACT	14q32.1	Sporadic	[99]
A2M	12p13.3-p12.3	Sporadic	[101]
MCP-1	17q11.2-q12	Sporadic	[103, 104]
RANTES	17q11.2-q12	Sporadic	[102]
CCR2	3p21.31	Sporadic	[105, 106]
CCR5	3p21	Sporadic	[105, 106]
IP-10	4q21	Sporadic	[107]
NOS3	7q36	Sporadic	[108]
NOS1	12q22	Sporadic	[116]

1.2. Inflammation in AD Pathogenesis

The fibrillar deposition of extracellular A β is closely associated with a neuroinflammatory response, which includes a local upregulation of acute-phase proteins, complement fragments, cytokines and other inflammatory mediators [9]. So far, epidemiological studies suggested that an inflammatory process contributes to AD pathology. Perspective case-cohort studies showed that higher serum levels of certain acute-phase proteins are a risk factor for the development of AD [10-12]. Moreover, epidemiological studies indicate that longstanding use of non-steroidal anti-inflammatory drugs can prevent or delay the development of AD [13-14]. Despite these studies, however, treatment of AD patients with anti-inflammatory drugs failed to demonstrate clinical benefits [15].

Microglial cells are the major producers of inflammatory factors. Recent studies demonstrated that during the early

stages of AD pathogenesis activated microglia were clustered within classic (dense-cored) plaques in the AD neocortex [16]. These plaques showed strong immunostaining for complement factor C1q and serum amyloid P component (SAP). Plaque-associated factors C1q and SAP may trigger microglia to secrete high levels of proinflammatory cytokines [2].

1.3. Cytokines and Alzheimer’s Disease

Activated microglial cells colocalize with A β , and *in vitro* studies demonstrated that A β induces the production of Tumor Necrosis Factor (TNF) α in such cells [17]. This cytokine is a pleiotropic factor acting as an important mediator of inflammatory responses in a variety of tissues. Levels of TNF α in cerebrospinal fluid (CSF) from AD patients are 25-fold higher than in CSF from age-matched controls [18], suggesting a role for inflammation in neurodegeneration. Nevertheless, other findings demonstrated a protective effect

of TNF α , as it likely protects neurons against A β triggered cytotoxicity [19]. Recently, the tumor necrosis factor type 1 death receptor (TNFR1), which contributes to apoptosis, has been deleted in APP23 transgenic mice, which overexpress β APP, demonstrating an inhibitory effect on A β generation and plaque formation in the brain. Moreover, deletion of TNFR1 leads to reduced β -secretase levels and activity [20].

Interleukin-1 (IL-1) exerts pleiotropic actions by binding to its receptor IL-1R and has been identified as a mediator in several forms of neurodegeneration. In AD, an increased production of IL-1 has been demonstrated by immunohistochemistry. In particular, it is expressed by microglia localized around amyloid deposits, possibly participating to plaque formation [21].

Interleukin-6 (IL-6) binds to a specific receptor activating an intracellular kinase-based signal pathway. Conflicting results have been reported with regard to IL-6 levels in serum and CSF of AD patients. However, it has been shown that its mRNA levels are increased in the entorhinal cortex and the superior temporal gyrus of AD patients [21]. Interestingly, previous studies demonstrated a large increase in endogenous IL-6 bioactivity in response to ischemia, as well as a marked neuroprotection produced by exogenous IL-6, thus suggesting that this cytokine is an important inhibitor of neuronal death during cerebral ischemia [22].

Microglial-produced inflammatory cytokines have neurophatic as well as neuroprotective actions. For instance, whereas excess levels of TNF α might cause neurotoxicity, low-dose TNF α could, alternatively, trigger the neuroprotective and/or anti-apoptotic genes [23]. The role of glial cells is to support and sustain proper neuronal function and microglia are no exception to this general principle. In acutely injured central nervous system (CNS) microglia have a neuroprotective and pro-regenerative role [24]. Therefore, the primary mode of action of microglia seems to be CNS protection. However, upon excessive or sustained activation, microglia could significantly contribute to chronic neuropathologies, leading to neurotoxicity [2].

Additional investigated cytokines are IL-11 and leukemia inhibitory factor (LIF), all belonging to the family of IL-6-type cytokines. All IL-6-type cytokines have overlapping bioactivities and share a common helical framework [25]. Intracellular signalling activated by these cytokines requires either homodimerization of their common signal transducing receptor subunit gp130 or heterodimerization of gp130 with a further β -receptor component, such as LIF (LIFR). Interleukin-11 mean levels were significantly increased in AD and Frontotemporal Lobar Degeneration (FTLD) as compared with controls, whereas CSF LIF levels were not detectable either in patients or controls [26]. In accordance with previous results [27], in AD patients, a significantly positive correlation between MMSE scores and IL-11 CSF concentration was observed [26].

In contrast with the previously described cytokines, Transforming Growth Factor beta (TGF- β) has mainly an anti-inflammatory action. Several data show that its levels are increased in the brain of AD patients, as well as in plasma and CSF. Moreover, TGF- β was also found both in amyloid plaques and tangles [21]. TGF- β 1 drives the produc-

tion of A β 40/42 by astrocytes, leading to A β production in TGF- β 1 transgenic mice. Notably, TGF- β 1 induces the overexpression of the APP in astrocytes but not in neurons, involving a highly conserved TGF- β 1 responsive element in the 5'-UTR. In addition, TGF- β 1 potentiates A β production also in human astrocytes, possibly enhancing the formation of A β plaques in the brain of patients with AD [28].

Besides TGF- β 1, a number of cytokines play a role in the regulation of APP expression in non neuronal cells. *In vitro* studies in astrocytes demonstrated that the 5'-UTR of the APP gene can respond to the stimulation of IL-1 α , IL-1 β , TGF- β 1 and TNF- α 1, which likely regulate APP transcription *via* regulatory elements present in the APP promoter and 5'-UTR [29]. The regulation of APP is a complex event, and, together with cytokines, other factors influence its expression. In particular, copper, zinc and iron were shown to accelerate the aggregation of A β by interacting with Iron-Responsive Elements (IRE) in the 5'-UTR of the APP gene [30]. These findings encouraged the development of chelators as a new therapeutic strategy for the treatment for the treatment of AD, together with non steroidal anti-inflammatory drugs and vaccine [30].

Recently, pro-inflammatory cytokine levels have been evaluated in Peripheral Blood Mononuclear Cells (PBMC) from 691 cognitively intact community-dwelling participants. Adjusting for clinical covariates, individuals in the top two tertiles of PBMC production of IL-1 or in the top tertile of PBMC production of TNF- α were at increased risk of developing AD compared with the lowest tertile. Therefore, the higher spontaneous production of these cytokines by PBMC may be a marker of future risk of AD in older individuals [31].

In conclusion, a better understanding of the mechanisms leading to A β production and neuroinflammation could not only clarify the pathogenetic steps leading to AD, but also facilitate the development of disease-modifying treatment for AD.

1.4. Chemokines and Alzheimer's Disease

Additional cytokines recently demonstrated to exert a role in AD are named chemokines. These are low molecular weight chemotactic cytokines that have been shown to play a crucial role in early inflammatory events. Based on the arrangement of cysteine residues, they are divided into two main groups: CXC or α -chemokines, i.e Interferon- γ -inducible Protein-10 (IP-10) and Interleukin-8 (IL-8), responsible for attracting neutrophils, and CC or β -chemokines, i.e Monocyte Chemotactic Protein-1 (MCP-1), and Macrophage Inflammatory Protein-1 α and β (MIP-1 α and β), which act basically on monocytes, but also stimulate the recruitment of basophils, eosinophils, T-cells and NK-cells [32]. In addition to their chemotactic effect in the immune system, they modulate a number of biological responses, including enzyme secretion, cellular adhesion, cytotoxicity, tumor cell growth and T-cell activation [33].

Upregulation of a number of chemokines has been associated with AD pathological changes [34]. IP-10 immunoreactivity was markedly increased in reactive astrocytes in AD brains, as well as the level of its expression. Astrocytes posi-

tive for IP-10 were found to be associated with senile plaques and showed an apparently coordinated upregulation of MIP-1 β [35, 36]. Recently, chemokine levels were detected in CSF from AD patients as well as subjects with MCI. A significant increase of IP-10 was observed in mild as compared with severe AD patients. Notably, similarly to mildly impaired AD, IP-10 increased levels were also found in amnesic MCI patients versus controls [27]. Regarding MCP-1 and IL-8, significantly higher levels were found in all AD patients as compared with healthy subjects, and highest peaks were observed in mild AD and MCI [27].

The deposition of A β , known to activate microglia to produce proinflammatory cytokines, may be responsible for the accumulation of IP-10 found in AD patients. In fact, the genomic organization of IP-10 gene shows the presence, in the promoter region, of critical regulatory sequences responding to IFN γ and TNF α independently activated factors, which lead to the transcriptional activation of the gene. Therefore, it is conceivable that the increased IP-10 levels observed in mild AD patients could be linked to amyloid deposition [27]. IP-10 increase can be restricted to an early stage of AD, when proinflammatory events are thought to play a more important role in disease development. The same trend has been observed also considering MCP-1 and IL-8 levels, strengthening the hypothesis that intrathecal inflammation precedes the development of AD, and represents an initiating factor of the disease rather than a late consequence [27].

With regard to a possible use of chemokine to easily predict evolution from MCI to AD, few investigation in serum have been so far carried out, despite a growing body of evidence supporting the hypothesis that some peripheral biochemical modifications also occur very early during AD pathogenesis. For instance, serum MCP-1 levels have been demonstrated to be increased in MCI subjects, similarly to findings described in the CSF [37]. Notably, CSF MCP-1 levels in patients studied were higher than the correspondent serum levels, and the Brain Blood Barrier (BBB) was intact, as shown by normal IgG indices. Thus, these data strongly suggest that peripheral modifications of MCP-1 levels occur early during AD development, when the clinical manifestation of the disease is not already clearly defined. Conversely, IP-10 serum levels were not increased in AD patients, but were found to correlate with aging [38].

In conclusion, these findings confirm that cytokines and chemokines have a crucial role in pathogenesis and progression of AD, and hopefully will be of help in the next future for early identification of individuals who more likely will develop AD, possibly in combination with other biomarkers.

2. INFLAMMATION AND FRONTOTEMPORAL LOBAR DEGENERATION

2.1. Clinical and Neuropathological Features

Among other non-AD dementias, the most frequent neurodegenerative disease is represented by FTLD [39, 40]. The most typical deficits in early AD involve episodic memory, while distinctive features in FTLD concern behavior, including disinhibition, loss of social awareness, overeating and

impulsiveness. Despite profound behavioral changes, memory is relatively spared [41]. Conversely to AD, which is more frequent in women, FTLD has an equal distribution among men and women, and age at onset is typically 45-65 years, with a mean in the 50s [42] (Table 1). The current consensus criteria [43] identify three clinical syndromes: Frontotemporal dementia (FTD), Progressive nonfluent Aphasia (PA) and Semantic Dementia (SD), which reflect the clinical heterogeneity of FTLD (Table 3). FTD is characterized by behavioral abnormalities, whereas PA is associated with progressive loss of speech, with hesitant, nonfluent speech output [44], and SD is associated with loss of knowledge about words and objects. This variability is determined by the relative involvement of the frontal and temporal lobes, as well as by the involvement of right and left hemispheres [45].

Table 3. Classification and Characteristics of FTLD. Upper Panel: According to Neary *et al.* (1998). Lower Panel: According to the Anatomical Involvement

<ul style="list-style-type: none"> •FTD– Disinhibition, +/- fasciculations •Progressive non-fluent aphasia <ul style="list-style-type: none"> – Agrammatism, phonemic paraphasia, anomia – Late mutism •Semantic dementia <ul style="list-style-type: none"> – Semantic aphasia (fluent, empty, semantic paraphasia) – Associative agnosia
<ul style="list-style-type: none"> •Left temporal lobe variant <ul style="list-style-type: none"> – Aphasia •Right temporal lobe variant <ul style="list-style-type: none"> – Irritability, impulsiveness – Bizarre alterations in dress – Limited and fixed ideas – Abnormal affect – Heightened visual awareness

From a neuropathological point of view, FTLD is characterized by intracellular deposition of abnormally phosphorylated tau protein, named Pick’s bodies, responsible for neuronal death [41].

FTLD is a heterogeneous disease characterized by a strong genetic component in its aetiology as up to 40% of patients report a family history of the disease in at least one extra family member [46]. In 1994 an autosomal dominantly inherited form of FTD with parkinsonism was linked to chromosome 17q21.2 [47]. Subsequently, other familial forms of FTD were found to be linked to the same region [48-50] resulting in the denomination “Frontotemporal dementia and parkinsonism linked to chromosome 17” (FTDP-17) for this class of diseases. All cases of FTDP-17 have so far shown a filamentous pathology made of hyperphosphorylated tau protein. Currently, 41 different mutations in the *MAPT* gene have been described in totally 117 families (<http://molgen-www.ua.ac.be>). Nevertheless, there have been reports of numerous families with autosomal dominant FTLD that are genetically linked to the same region of chr17q21 that contains *MAPT* but in which no pathogenic mutations can be identified, despite extensive analysis of this gene [51-53]. The neuropathological phenotype in these

families was characterized by ubiquitin immunoreactive neuronal inclusions. Sequence analysis of the whole *MAPT* region failed to find a mutation and tau protein appears normal in these families. Moreover the minimal region containing the disease gene for this group of families was approximately 6.2 Mb in physical distance, strongly arguing against *MAPT* and pointing to another gene. Systematic candidate gene sequencing of all remaining genes within the minimal candidate region was performed and after sequencing 80 genes, including those prioritized on known function, the first mutation in progranulin gene (*PGRN*) was identified [54, 55].

Subsequently, these results have been replicated and improved. At present, there is no obvious mechanistic link between the mutations in *MAPT* and *PGRN*, currently assuming that their proximity on chromosome 17 is simply a coincidence. Progranulin is known by several different names including granulin, acrogranin, epithelin precursor, proepithelin and prostate cancer (PC) cell derived growth factor [56]. The protein is encoded by a single gene on chromosome 17q21, which produces a 593 amino acid, cysteine rich protein with a predicted molecular weight of 68.5 kDa. Progranulin and the various granulin peptides are implicated in a range of biological functions including development, wound repair and inflammation by activating signaling cascades that control cell cycle progression and cell motility [56]. Excess progranulin appears to promote tumor formation and hence can act as a cell survival signal. Despite the increasing literature on the function of progranulin, its role in neuronal function and survival remains unclear. In the human brain, *PGRN* is expressed in neurons but is also highly expressed in activated microglia [55].

Since the original identification of null-mutations in FTLN in 2006, additional novel mutations have been reported, spanning most exons, and to date more than 44 *PGRN* mutations have been described [57-65]. These mutations account for about 30-40% of cases, whereas remainders are sporadic and likely influenced by several interacting genes (Table 4).

2.2. Inflammatory Factors in Sporadic FTLN

Recent evidence suggests that inflammatory mediators could have a role also in sporadic FTLN, as upregulation of TNF α and downregulation of TGF β have been demonstrated in CSF from patients with FTD [66]. Regarding chemokines, no differences were found in CSF IP-10 levels, whereas, similarly to AD, MCP-1 levels were increased in FTLN as compared with healthy subjects. A similar pattern was observed considering IL-8 levels. No significant differences in chemokine levels were observed among FTD, PA and SD

subtypes [67]. The increase in these cytokines and chemokines were not related to a disturbance of the blood brain barrier function or leakage through it, nor were they related to age or gender. Furthermore, no correlation was found between CSF and serum levels. It is likely conceivable that the increased IP-10 levels observed in AD patients, compared with FTLN, could be linked to A β deposition, which occurs typically in AD and less in FTLN [67, 68]. Indeed, a possible protective role of MCP-1 has been suggested as it is involved in the regeneration of neural tissue *via* the induction of differentiation and of neurotrophic factors such as basic fibroblast growth factor (bFGF) by astrocytes and microglia [69]. Similarly, IL-8 increase could be related to compensative and reparative mechanisms as well, through IL-8 capability to promote neuronal survival [70].

A positive effect could be exerted by TNF α as well. In fact this cytokine, currently known to be proinflammatory and to induce apoptosis, activate the transcription of TGF β [71], which acts as anti-inflammatory factor by inhibiting IL-6 and IL-1 β production by astrocytes and suppressing the activation and proliferation of microglia [72]. Thus, in patients with FTD, the increased levels of TNF α may trigger the production of TGF β by a negative feedback mechanism which counteracts the proinflammatory effect of TNF α [66].

3. INFLAMMATION IN AMYOTROPHIC LATERAL SCLEROSIS

3.1. Clinical Features

Amyotrophic Lateral Sclerosis (ALS) is characterized by a progressive loss of upper and lower motor neurons in the spinal cord, brain stem and cerebral cortex, culminating in respiratory failure. Its prevalence is 1:20,000 in the general population, and incidence increases with age, with peaks between 50 and 55 years of age.

The genetic component is present in approximately 10% of ALS cases which are familial in nature (FALS), and in about 20% of these families, the disease is linked to mutations in the *SOD1* gene [73-74], which is located on chromosome 21 (Table 5). SOD1 is a 153-amino acid protein, containing one copper and one zinc, and is predominantly located in the cytoplasm as a homodimer. It is involved in the detoxification of superoxide, leading to the generation of oxygen and hydrogen peroxide, which can then be cleared by catalase and glutathione peroxidase.

To date, more than 110 different mutations have been identified in the *SOD1* gene in familial ALS [75]. Most of these mutations are missense, only few of them are deletions and insertions that result in prematurely terminated SOD1 protein. The expression of a mutant SOD1 polypeptide is

Table 4. Causative Genes of Familial FTLN and Genes Claimed to be Potential Susceptibility or Modifier Factors for FTLN

Gene	Chromosome	Association	Reference
MAPT	17q21.1	Familial	[48-50]
PSEN1	14q24.3	Familial	[143]
PGRN	17q21.31	Familial	[54-55]
APOE	17q21.1	Sporadic	[133]

Table 5. Causative Genes of FALS and Genes Claimed to be Potential Susceptibility or Modifier Factors for SALS

Gene-protein	Chromosome	Association	Reference
ALS1 -SOD1	21q22	Familial	[73]
ALS2- Alsin	2q33	Familial	[144]
ALS3	18q21	Familial	[145]
ALS4-Senataxin	9q34	Familial	[77]
ALS5	15q15.1-q21.1	Familial	[146]
ALS6	16q12	Familial	[147]
ALS7	20ptel-p13	Familial	[148]
ALS8 VAPB	20q13.83	Familial	[149]
ALS-FTD	9q21-22	Familial	[78]
ALS with dementia tau	9q21-22	Familial	[150]
Progressive LMN disease dynactin	2p13	Familial	[76]
NEFH	22q12.1-q13.1	Sporadic	[151]
VEGF-Vascular endothelial growth factor	6p12	Sporadic	[152]
SMN1	5q12.2-q13.3	Sporadic	[153]
SMN2	5q12.2-q13.3	Sporadic	[154]
APOE*4-Apolipoprotein E	19q13.2	Sporadic	[155]
EAAT2	11p13-p12	Familial	[156]
GluR2	4q32-q33	Sporadic	[157]

necessary to cause the ALS phenotype. However even after many years of investigation, the exact mechanism of SOD1-mediated pathogenesis remains uncertain. In recent years additional gene mutations have been found for FALS, including the *ALS2* gene, which encodes for a novel protein with homology to guanine-nucleotide exchange factors [75]. Loss of *ALS2* leads to a slowly progressing motor neuron disease that appears during the first decade of life. Mutations of the dynactin gene have also been found in a slowly progressive, autosomal dominant form of ALS [76]. Additional genetic markers for familial forms of ALS include the senataxin gene (*ALS4*) in autosomal dominant juvenile ALS [77], and a locus on chromosome 9q21 to five families with ALS with frontotemporal dementia [78] (Table 5).

Concerning sporadic ALS (SALS), several pathogenetic hypotheses have been proposed, including oxidative stress, mitochondrial dysfunction, excitotoxic damage and abnormalities of protein folding [79].

3.2. Inflammatory Factors in Sporadic ALS

Data obtained in ALS animal models (mutant SOD1 transgenic rodents) as well as in humans suggest that cytokines and growth factors play a role in the pathogenesis of the disease. In the spinal cord of either patients or SOD1 mice, motor neuron loss and dramatic increase in activated microglia, reactive astrocytes and dendritic cells have been shown [80, 81]. Among cytokines, MCP-1 [81-83] IL-6 [84], TNF- α [85], and TGF- β [86] have been shown to be upregulated in CSF or serum. A recent study carried out with the novel multiplex fluorescent bead-based immunoassay technique simultaneously measured multiple cytokines/chemokines, including IL-1 β , IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12(p70), IL-13, IL-17, interferon (IFN)- γ , TNF- α , G-CSF, MCP-1 and MIP-1 β in CSF from ALS patients [79]. Among them, G-CSF, MCP-1 and IL-5 levels were significantly higher in patients with ALS than in patients with other non-

inflammatory neurological diseases (OND), whereas IL-10 levels were significantly decreased in patients with ALS as compared with OND. Moreover, in CSF, the concentration of MCP-1 was negatively correlated with the revised ALS functional rating scale (ALSFRS-R) score and positively correlated with the disease progression rate [79]. Immunoreactivity for G-CSF was strongly enhanced in cytoplasm of several reactive astrocytes in the anterior horn of ALS cases as compared with controls [79]. In the same study, G-CSF was demonstrated to exert a protective effect on a cell line with motor neuron characteristics, thus raising the hypothesis that G-CSF may promote motor neuron survival.

4. INFLAMMATORY MOLECULES AS RISK FACTORS FOR NEURODEGENERATION

Genetic variability is a prominent characteristic of many neurodegenerative disorders. Risk genes are likely to be numerous, displaying intricate patterns of interaction with each other as well as with non-genetic variables, and-unlike classical Mendelian ("simplex") disorders, exhibit no simple mode of inheritance. Mainly due to this reason, the genetics of these diseases has been labeled "complex" [87]. The ability to genetically map complex disorders has been facilitated by technological improvement in identifying and genotyping polymorphic DNA markers. The current trend is to use single-nucleotide polymorphisms (SNPs), the most frequent genetic polymorphisms. The search for susceptibility genes in complex diseases centers on two major techniques: linkage mapping and candidate gene approach. Linkage analysis attempts to identify a region (locus) of the chromosome or regions (loci) in the genome associated with the disease or trait by identifying which alleles in the loci are segregating with the disease in families, whereas genetic association analysis examines whether affected individuals share the variant allele more often than control subjects do [88].

Several genes have been associated with sporadic AD (SAD, Table 2). The gene mainly related to SAD is the *APOE* [89] which is located in chromosome 19q13.32 and was initially identified by linkage analysis [90]. The relationship between *APOE* and AD has been confirmed in more than 100 studies conducted in different populations. The gene has three different alleles, *APOE*2*, *APO*3* and *APOE*4*. The *APOE*4* allele is the variant associated with AD. Longitudinal studies in Caucasian populations have shown that carriers for one *APOE*4* allele have a two-fold increase in the risk for AD [91]. The risk increases in homozygotes for the *APOE*4* allele, and this allelic variant is also associated with an earlier onset of the disease. Interestingly, *APOE*4* likely interacts with other genes to increase the susceptibility to AD. In particular, an interaction with two polymorphisms in APH-1a and APH-1b, both subunits of the gamma-secretase complex, has been recently demonstrated [92].

Several linkage studies have been performed, giving rise to a number of candidate susceptibility loci at chromosomes 1, 4, 6, 9, 10, 12 and 19. In particular the most promising loci have been found at chromosome 9 and 10 [93, 94].

Also, a large number of candidate genes studies have been performed in order to search a robust risk factor for the sporadic form of the disease. Studies were mainly focused in genes clearly involved in the pathogenesis of AD such as genes encoding for inflammatory molecules or gene involved in the oxidative stress cascade, both considered major factors in AD pathology (Table 2). One of the strongest evidence of the role played by genetic variants in inflammatory agents to increase the risk of AD involves the IL1 complex which is located at chromosome 2q14-21 and includes IL1- α , IL1- β , and IL1R antagonist protein (IL-1Ra), all of which have significant polymorphisms found to be associated with AD in several case-control studies carried out in different populations [95-97]. Several polymorphisms in *IL-6* which is a potent inflammatory cytokine have also been investigated. The *IL6* gene is located at chromosome 7p21 and polymorphisms exist in the -174 promoter region and in the region of a variable number of tandem repeats (VNTR) which is located in the 3' untranslated region. Both of them have been found associated with AD in case-control studies [98, 99]. Investigation of tumor *TNF α* polymorphisms was initiated because genome screening had suggested a putative association of AD with a region on chromosome 6p21.3, which lies within 20 centimorgans of the *TNF α* gene. Furthermore, other polymorphisms located in the promoter region of *TNF α* have been associated with autoimmune and inflammatory diseases [100]. α 1-Antichymotrypsin (*ACT*) is an acute-phase reactant produced by activated astrocytes and is elevated in brains affected with AD. The combined effect of *ACT* and *IL1 β* polymorphisms has been demonstrated by Licastro *et al.* [99].

As with *TNF α* , investigation, of the role of α -2macroglobulin (*A2M*) was initiated as a result of screening studies of the genome. In this case, linkage was found in the region of chromosome 1p, where *A2M* and its low-density lipoprotein receptor are found. Blacker *et al.* [101] tested for association of polymorphisms with AD showing a strong involvement of this gene in AD.

In addition, polymorphisms in chemokines have been investigated with regard to susceptibility of AD. In particular, MCP-1 and RANTES have been widely screened in different neurodegenerative diseases [102]. The distribution of the *A-2518G* variant was determined in different AD populations with concordant results [103, 104] showing no evidence for association of this variant in AD compared with controls. Moreover, a significant increase of MCP-1 serum levels in AD carrying at least one *G* mutated allele was found [104]. Therefore, the *A-2518G* polymorphism does not seem to be a risk factor for the development of AD, but its presence correlates with higher levels of serum MCP-1.

RANTES promoter polymorphism -403 *A/G*, found to be associated with several autoimmune diseases, was examined in AD population, failing to find significant differences between patients and controls [102].

The genes *CCR2* and *CCR5*, encoding for the receptors of MCP-1 and RANTES, respectively, have been also screened for association with AD. The most promising variants involve a conservative change of a valine with an isoleucine at codon 64 of *CCR2* (*CCR2-64I*) and a 32-bp deletion in the coding region of *CCR5* (*CCR5 Δ 32*), which leads to the expression of a non functional receptor. A decreased frequency and an absence of homozygous for the polymorphism *CCR2-64I* were found in AD, thus suggesting a protective effect of the mutated allele on the occurrence of the disease [105]; conversely, no different distribution of the *CCR5 Δ 32* deletion in patients compared with controls were shown [105, 106].

A further chemokine recently tested for susceptibility with AD is IP-10. A mutation scanning of the gene coding region has been performed in a restricted number of AD patients searching for new variants. The analysis demonstrated the presence of two previously reported polymorphisms in exon 4 (*G/C* and *T/C*), which are in complete linkage disequilibrium, as well as a novel rare one in exon 2 (*C/T*). Subsequently these SNPs have been tested in a wide case-control study, but no differences in haplotype frequencies were found [107].

Other genes under investigation are related to oxidative stress, a process closely involved in AD pathogenesis. In this regard, genes coding for the nitric oxide synthase (NOS) complex have been screened. The common polymorphism consisting in a *T/C* transition (*T-786C*) in *NOS3*, previously reported to be associated with vascular pathologies, has been tested in AD, but no significant differences with controls were found [108]. Nevertheless, expression of *NOS3* in PBMC either from patients or controls seems to be influenced by the presence of the *C* allele, and is likely to be dose dependent, being mostly evident in homozygous for the polymorphic variant. The influence of the polymorphism on *NOS3* expression rate supports the hypothesis of a beneficial effect exerted in AD by contributing to lower oxidative damage [108].

An additional variant in *NOS3* gene has been extensively investigated in AD patients, although results are still controversial. It is a common polymorphism consisting in a single base change (*G894T*), which results in an aminoacidic substitution at position 298 of *NOS3* (Glu298Asp). Dahiya *et*

al. [109] determined the frequency of the Glu298Asp variant in a two-stage case-control study, showing that homozygous for the wild-type allele were more frequent in late onset AD. However, studies in other populations failed to replicate these results [110-113].

Recently Guidi *et al.* [114] correlated this variant with total plasma homocysteine (tHcy) levels in 97 patients and 23 controls, on the basis of a previous study from Brown *et al.* [115] who demonstrated, in two independent healthy populations, that subjects homozygous for the mutation tend to have higher tHcy concentrations compared with Glu/Asp and Glu/Glu subjects.

The Glu/Glu genotype was correlated with higher levels of tHcy and its frequency was increased in AD patients [114]. Thus, the mechanism by which this genotype contributes to increase the risk in developing AD could be mediated by an increase of tHcy levels.

However, *NOS1* is the isoform most abundantly expressed in the brain. Genetic analyses demonstrated that the double mutant genotype of the synonymous *C276T* polymorphism in exon 29 of the *NOS1* gene represents a risk factor for the development of early onset AD [116], whereas the dinucleotide polymorphism in the 3'UTR of *NOS1* is not associated with AD [117]. To date, the promoter region of *NOS1*, located approximately 200 kb upstream of this polymorphism, has not been investigated for susceptibility to AD. Due to this reason and to further explore a possible association of *NOS1* polymorphisms with AD, the distribution of a functional polymorphisms and a variable number of tandem repeats (VNTR) was analyzed in a case-control study, which tested 184 AD patients as well as 144 healthy subjects [118]. The functional variant considered is located in exon 1c, which is one of the nine alternative first exons (named 1a-1i), resulting in *NOS1* transcripts with different 5'-untranslated regions [119]. Three SNPs have been identified in exon 1c, but only the *G-84A* variant displays a functional effect, as the *A* allele decreases transcription levels by 30% in in-vitro models [120]. Regarding exon 1f, a variable number of tandem repeats (VNTR) polymorphism has been recently reported in its putative promoter region, termed *NOS1 Ex1f-VNTR*. This VNTR is highly polymorphic and consists of different numbers of dinucleotides (B-Q), which, according to their bimodal distribution, have been dichotomized in short (B-J) and long (K-Q) alleles for association studies [121]. Both Ex1c *G-84A* and Ex1f-VNTR are associated with psychosis and prefrontal functioning in patients with schizophrenia [121]. Notably, both Ex1c and Ex1f transcripts are found in the hippocampus and the frontal cerebral cortex [121], i.e. brain regions implicated in the pathogenesis of schizophrenia as well as AD. The presence of the short (*S*) allele of *NOS1 Ex1f-VNTR* resulted to be a risk factor for the development of AD [118]. The effect is cumulative, as in *S/S* carriers the risk is doubled. Most interestingly, the effect of this allele is likely to be gender specific, as it was found in females only. In addition, the *S* allele was shown to interact with the *APOE*4* allele both in males and females, increasing the risk to develop AD by more than 10 fold [118]. Thus, *NOS1* seems to be a risk factor for AD, but only in female population. This could be explained by a possible interaction

with other genes or with additional environmental factors present in females but not males.

The best well-known risk factor for late onset sporadic AD, *APOE*4*, has also been considered as a risk factor for sporadic FTLN (Table 4). A number of studies suggested an association between FTLN and *APOE*4* allele [122-127]. Other Authors however, did not replicate these data [128-130]. Recent findings demonstrated an association between the *APOE*4* allele and FTLN in males, but not females [131], possibly explaining the discrepancies previously reported. An increased frequency of the *APOE*4* allele was described in patients with SD compared to those with FTD and PPA [129]. Concerning the *APOE*2* allele in the development of FTLN, heterogeneous data have been obtained in different populations. Bernardi *et al.* [127] showed a protective effect of this allele towards FTLN, whereas other Authors failed to do so [129-132]. Despite these results, a meta-analysis comprising a total of 364 FTD patients and 2671 controls (CON) demonstrated an increased susceptibility to FTD in *APOE*2* carriers [133].

Regarding *MAPT*, besides pathogenic mutations, several polymorphisms have been reported to date. A number of these polymorphisms are in complete linkage disequilibrium and inherited as 2 distinct haplotypes, named H1 and H2. They differ in nucleotide sequence and intron size, but are identical at the amino acid level. Up to now, H1 *MAPT* haplotype was found to be associated with different forms of tauopathies including FTD, progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) [134-139].

Regarding sporadic ALS (SALS), a number of potential susceptibility and modifier loci have been identified, several of them involved in oxidative stress (Table 5).

In conclusion, regarding sporadic form of neurodegenerative diseases several polymorphisms have been described in cytokine and chemokines genes as well as in gene involved in oxidative stress pathway. These allelic variants might increase the risk to develop neurodegenerative diseases, but are insufficient to provoke the disease alone. However, the overall risk to develop these diseases may be profoundly affected by the combination of these multiple high risk alleles. Therefore, an accurate genetic screening of polymorphisms conferring increased susceptibility to neurodegenerative diseases could be of help for identifying populations which are more at risk to develop the disease.

REFERENCES

- [1] Griffin WS. Inflammation and neurodegenerative diseases. *Am J Clin Nutr* 83(suppl): 470S-474S (2006).
- [2] Hoozemans JJM, Veerhuis R, Rozemuller JM and Eikelenboom P. Neuroinflammation and regeneration in the early stages of Alzheimer's disease pathology. *Int J Neurosci* 24: 157-165 (2006).
- [3] Loffler J and Huber G. Beta-amyloid precursor protein isoforms in various rat brain regions and during brain development. *J Neurochem* 59: 1316-1324 (1992).
- [4] Graham DI, Gentleman SM, Nicoll JA, Royston MC, McKenzie JE, Roberts GW, *et al.* Altered beta-APP metabolism after head injury and its relationship to the aetiology of Alzheimer's disease. *Acta Neurochir Suppl* 66: 96-102 (1996).
- [5] Sheng JG, Boop FA, Mraz RE and Griffin WS. Increased neuronal beta-amyloid precursor protein expression in human temporal lobe

- epilepsy: association with interleukin-1 alpha immunoreactivity. *J Neurochem* 63: 1872-1879 (1994).
- [6] Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG and Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 56: 303-308 (1999).
- [7] Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, *et al.* Mild Cognitive Impairment. *Lancet* 367: 1262-1270 (2006).
- [8] Markesbery WR, Schmitt FA, Kryscio RJ, Davis DG, Smith CD, Wekstein DR. Neuropathologic substrate of mild cognitive impairment. *Arch Neurol* 63: 38-46 (2006).
- [9] Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, *et al.* Inflammation and Alzheimer's disease. *Neurobiol Aging* 21: 383-421 (2000).
- [10] Yaffe K, Lindquist K, Penninx BW, Simonsick EM, Pahor M, Kritchevsky S, *et al.* Inflammatory markers and cognition in well-functioning African-American and white elders. *Neurology* 61(1): 76-80 (2003).
- [11] Engelhart MJ, Geerlings MI, Meijer J, Kiliaan A, Ruitenberg A, van Swieten JC, *et al.* Inflammatory proteins in plasma and the risk of dementia: the Rotterdam study. *Arch Neurol* 61: 668-672 (2004).
- [12] Dik MG, Jonker C, Hack CE, Smit JH, Comijs HC and Eikelenboom P. Serum inflammatory proteins and cognitive decline in older persons. *Neurology* 64: 1371-1377 (2005).
- [13] McGeer PL, Schulzer M and McGeer EG. Arthritis and anti-inflammatory agents as possible protective factors for Alzheimer's disease: a review of 17 epidemiologic studies. *Neurology* 47: 425-432 (1996).
- [14] in 't Veld BA, Ruitenberg A, Hofman A, Launer LJ, van Duijn CM, Stijnen T, *et al.* Nonsteroidal antiinflammatory drugs and the risk of Alzheimer's disease. *N Engl J Med* 345: 1515-1521 (2001).
- [15] van Gool WA, Aisen PS and Eikelenboom P. Anti-inflammatory therapy in Alzheimer's disease: is hope still alive? *J Neurol* 250: 788-792 (2003).
- [16] Veerhuis R, Van Breemen MJ, Hoozemans JM, Morbin M, Ouladhadj J, Tagliavini F, *et al.* Amyloid beta plaque-associated proteins C1q and SAP enhance the Abeta 1-42 peptide-induced cytokine secretion by adult human microglia *in vitro*. *Acta Neuropathol* 105: 135-144 (2003).
- [17] Meda L, Cassatella MA, Szendrei GI, Ottovs L Jr, Baron P, Villalba M, *et al.* Activation of microglial cells by beta-amyloid protein and interferon-gamma. *Nature* 374: 647-650 (1995).
- [18] Tarkowski E, Wallin A, Blennow K and Tarkowski A. Intracerebral production of tumor necrosis factor-alpha, a local neuroprotective agent, in Alzheimer disease and vascular dementia. *J Clin Immunol* 19: 223-230 (1999).
- [19] Barger SW, Hörster D, Furukawa K, Goodman Y, Kriegelstein L and Mattson MP. Tumor necrosis factors alpha and beta protect neurons against amyloid beta-peptide toxicity: evidence for involvement of a kappa B-binding factor and attenuation of peroxide and Ca²⁺ accumulation. *Proc Natl Acad Sci USA* 92: 9328-9332 (1995).
- [20] He P, Zhong Z, Lindholm K, Berning L, Lee W, Lemere C, *et al.* Deletion of tumor necrosis factor death receptor inhibits amyloid b generation and prevents learning and memory deficits in Alzheimer's mice. *J Cell Biol* 178(5): 829-841 (2007).
- [21] Cacquevel M, Lebeurrer N, Chéenne S and Vivien D. Cytokines in neuroinflammation and Alzheimer's disease. *Curr Drug Targets* 5: 529-534 (2004).
- [22] Loddick SA, Turnbull AV and Rothwell NJ. Cerebral interleukin-6 is neuroprotective during permanent focal cerebral ischemia in the rat. *J Cereb Blood Flow Metab* 18: 176-179 (1998).
- [23] Rozemuller JM and van Muiswinkel FL. Microglia and neurodegeneration. *Eur J Clin Invest* 30: 469-470 (2000).
- [24] Streit WJ. Microglia as neuroprotective, immunocompetent cells of the CNS. *Glia* 40: 133-139 (2002).
- [25] Taga T and Kishimoto T. Gp130 and the interleukin-6 family of cytokines. *Annu Rev Immunol* 15: 797-819 (1997).
- [26] Galimberti D, Venturelli E, Fenoglio C, Guidi I, Villa C, Bergamaschini L, *et al.* Intrathecal levels of IL-6, IL-11 and LIF in Alzheimer's disease and Frontotemporal Lobar Degeneration. *J Neurol*, in press.
- [27] Galimberti D, Schoonenboom N, Scheltens P, Fenoglio C, Bouwman F, Venturelli E, *et al.* Intrathecal chemokine synthesis in mild cognitive impairment and Alzheimer disease. *Arch Neurol* 63(4): 538-543 (2006).
- [28] Lesnè S, Docagne F, Gabriel C, Liot G, Lahiri DK, Buè L, *et al.* Transforming growth factor-β1 potentiates amyloid-β generation in astrocytes and in transgenic mice. *J Biol Chem* 278(20): 18408-18418 (2003).
- [29] Lahiri DK, Chen D, Vivien D, Ge YW, Greig NH and Rogers JT. Role of cytokines in the gene expression of amyloid β-precursor: identification of a 5'-UTR-binding nuclear factor and its implications in Alzheimer's disease. *J Alzheimers Dis* 5: 81-90 (2003).
- [30] Rogers JT and Lahiri DK. Metal and inflammatory targets for Alzheimer's disease. *Curr Drug Targets* 5(6): 535-551 (2004).
- [31] Tan ZS, Beiser AS, Vasan RS, Roubenoff R, Dinarello CA, Harris TB, *et al.* Inflammatory markers and the risk of Alzheimer's disease. *Neurology* 68(22): 1902-1908 (2007).
- [32] Scarpini E, Galimberti D, Baron P, Clerici R, Ronzoni M, Conti G, *et al.* IP-10 and MCP-1 levels in CSF and serum from multiple sclerosis patients with different clinical subtypes of the disease. *J Neurol Sci* 195: 41-46 (2002).
- [33] Mennicken F, Maki R, de Souza EB and Quirion R. Chemokines and chemokine receptors in the CNS: a possible role in neuroinflammation and patterning. *Trends Pharmacol Sci* 20: 73-78 (1999).
- [34] Xia MQ and Hyman BT. Chemokines/chemokine receptors in the central nervous system and Alzheimer's disease. *J Neurovirol* 5: 32-41 (1999).
- [35] Xia MQ, Qin SX, Wu LJ, Mackay CR and Hyman BT. Immunohistochemical study of the beta-chemokine receptors CCR3 and CCR5 and their ligands in normal and Alzheimer's disease brains. *Am J Pathol* 153: 31-37 (1998).
- [36] Xia MQ, Bacskai BJ, Knowles RB, Qin SX, and Hyman BT. Expression of the chemokine receptor CXCR3 on neurons and the elevated expression of its ligand IP-10 in reactive astrocytes: *in vitro* ERK1/2 activation and role in Alzheimer's disease. *J Neuroimmunol* 108: 227-235 (2000).
- [37] Galimberti D, Fenoglio C, Lovati C, Venturelli E, Guidi I, Corra B, *et al.* Serum MCP-1 levels are increased in mild cognitive impairment and mild Alzheimer's disease. *Neurobiol Aging* 27(12): 1763-8 (2006).
- [38] Galimberti D, Venturelli E, Fenoglio C, Lovati C, Guidi I, Scalabrini D, *et al.* IP-10 serum levels are not increased in Mild Cognitive Impairment and Alzheimer's disease. *Eur J Neurol* 14(4): e3-4 (2007).
- [39] Ratnavalli E, Brayne C, Dawson K and Hodges JR. The prevalence of frontotemporal dementia. *Neurology* 58: 1615-1621 (2002).
- [40] Scarpini E, Galimberti D and Bresolin N. Genetics and neurobiology of frontotemporal lobar degeneration. *Neurol Sci* 27 (Suppl 1): S32-34 (2006).
- [41] Hou CE, Carlin D and Miller BL. Non-Alzheimer's disease dementias: anatomic, clinical, and molecular correlates. *Can J Psychiatry* 49(3): 164-171 (2004).
- [42] Neary D, Snowden J and Mann D. Frontotemporal dementia. *Lancet Neurol* 4: 771-780 (2005).
- [43] Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, *et al.* Frontotemporal lobar degeneration. A consensus on clinical diagnostic criteria. *Neurology* 51: 1546-1554 (1998).
- [44] Scarpini E, Galimberti D, Guidi I, Bresolin N and Scheltens P. Progressive, isolated language disturbance: its significance in a 65-year-old-man. A case report with implications for treatment and review of literature. *J Neurol Sci* 240(1-2): 45-51 (2006).
- [45] Rosen HJ, Hartikainen KM, Jagust W, Kramer JH, Reed BR, Cummings JL, *et al.* Utility of clinical criteria in differentiating frontotemporal lobar degeneration (FTLD) from AD. *Neurology* 58: 1608-1615 (2002).
- [46] Snowden JS, Neary D and Mann DM. Frontotemporal dementia. *Br J Psychiatry* 180: 140-143 (2002).
- [47] Wilhelmsen KC, Lynch T, Pavlou E, Higgins M and Nygaard TG. Localization of disinhibition-dementia-parkinsonism-amyotrophy complex to 17q21-22. *Am J Hum Genet* 55(6): 1159-1165 (1994).
- [48] Hutton M, Lendon CL, Rizzu P, Baker M, Froelich S, Houlden H, *et al.* Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature* 393: 702-705 (1998).

- [49] Poorkaj P, Bird TD, Wijsman E, Nemens E, Garruto RM, Anderson L, *et al.* Tau is a candidate gene for chromosome 17 frontotemporal dementia. *Ann Neurol* 43: 815-825 (1998).
- [50] Spillantini MG, Murrell JR, Goedert M, Farlow MR, Klug A and Ghetti B. Mutation in the tau gene in familial multiple system tauopathy with presenile dementia. *Proc Natl Acad Sci USA* 95: 7737-7741 (1998).
- [51] Lendon CL, Lynch T, Norton J, McKeel DW Jr, Busfield F, Craddock N, *et al.* Hereditary dysphasic disinhibition dementia: a frontotemporal dementia linked to 17q21-22. *Neurology* 50: 1546-1555 (1998).
- [52] Rosso SM, Kamphorst W, de Graaf B, Willemsen R, Ravid R, Niermeijer MF, *et al.* Familial frontotemporal dementia with ubiquitin-positive inclusions is linked to chromosome 17q21-22. *Brain* 124: 1948-1957 (2001).
- [53] van der Zee J, Rademakers R, Engelborghs S, Gijselink I, Bogaerts V, Vandenberghe R, *et al.* A Belgian ancestral haplotype harbours a highly prevalent mutation for 17q21-linked tau-negative FTLD. *Brain* 129: 841-852 (2006).
- [54] Cruts M, Gijselink I, van der Zee J, Engelborghs S, Wils H, Pirici D, *et al.* Null mutations in progranulin cause ubiquitin-positive frontotemporal dementia linked to chromosome 17q21. *Nature* 442(7105): 920-924 (2006).
- [55] Baker M, Mackenzie IR, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, *et al.* Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. *Nature* 442(7105): 916-919 (2006).
- [56] He Z and Bateman A. Progranulin (granulin-epithelin precursor, PC-cell-derived growth factor, acrogranin) mediates tissue repair and tumorigenesis. *J Mol Med* 81(10): 600-612 (2003).
- [57] Boeve BF, Baker M, Dickson DW, Parisi JE, Giannini C, Josephs KA, *et al.* Frontotemporal dementia and parkinsonism associated with the IVS1+1G→A mutation in progranulin: a clinicopathologic study. *Brain* 129: 3103-3114 (2006).
- [58] Gass J, Cannon A, Mackenzie IR, Boeve B, Baker M, Adamson J, *et al.* Mutations in progranulin are a major cause of ubiquitin-positive frontotemporal lobar degeneration. *Hum Mol Genet* 15(20): 2988-3001 (2006).
- [59] Masellis M, Momeni P, Meschino W, Heffner R Jr, Elder J, Sato C, *et al.* Novel splicing mutation in the progranulin gene causing familial corticobasal syndrome. *Brain* 129: 3115-3123 (2006).
- [60] Pickering-Brown SM, Baker M, Gass J, Boeve BF, Loy CT, Brooks WS, *et al.* Mutations in progranulin explain atypical phenotypes with variants in MAPT. *Brain* 129: 3124-3126 (2006).
- [61] Snowden JS, Pickering-Brown SM, Mackenzie IR, Richardson AM, Varna A, Neary D, *et al.* Progranulin gene mutations associated with frontotemporal dementia and progressive non-fluent aphasia. *Brain* 129: 3091-3102 (2006).
- [62] Bronner IF, Rizzu P, Seelaar H, van Mil SE, Anar B, Azmani A, *et al.* Progranulin mutations in Dutch familial frontotemporal lobar degeneration. *Eur J Hum Genet* 15(3): 369-374 (2007).
- [63] Mesulam M, Johnson N, Krefft TA, Gass JM, Cannon AD, Adamson JL, *et al.* Progranulin mutations in primary progressive aphasia: the PPA1 and PPA3 families. *Arch Neurol* 64: 43-47 (2007).
- [64] Spina S, Murrell JR, Huey ED, Wassermann EM, Pietrini P, Barabbar MA, *et al.* Clinicopathologic features of frontotemporal dementia with Progranulin sequence variation. *Neurology* 68(11): 820-827 (2007).
- [65] Benussi L, Binetti G, Sina E, Gigola L, Bettecken T, Meitinger T, *et al.* A novel deletion in progranulin gene is associated with FTDP-17 and CBS. *Neurobiol Aging*. Dec 5; [Epub ahead of print] (2006).
- [66] Sjögren M, Folkesson S, Blennow K and Tarkowski E. Increased intrathecal inflammatory activity in frontotemporal dementia: pathophysiological implications. *J Neurol Neurosurg Psychiatry* 75: 1107-1111 (2004).
- [67] Galimberti D, Schoonenboom N, Scheltens P, Fenoglio C, Venturelli E, Pijnenburg YA, *et al.* Intrathecal chemokine levels in Alzheimer disease and frontotemporal lobar degeneration. *Neurology* 66: 146-147 (2006).
- [68] Iwatsubo T, Odaka A, Suzuki N, Mizusawa H, Nukina N and Ihara Y. Visualization of A beta 42(43) and A beta 40 in senile plaques with end-specific A beta monoclonals: evidence that an initially deposited species is A beta 42(43). *Neuron* 13: 45-53 (1994).
- [69] Kalehua AN, Nagel JE, Whelchel LM, Gides JJ, Pyle RS, Smith RJ, *et al.* Monocyte chemoattractant protein-1 and macrophage inflammatory protein-2 are involved in both excitotoxin-induced neurodegeneration and regeneration. *Exp Cell Res* 297: 197-211 (2004).
- [70] Araujo DM, Cotman CW. Trophic effects of interleukin-4, -7 and -8 on hippocampal neuronal cultures: potential involvement of glial-derived factors. *Brain Res* 600: 9-55 (1993).
- [71] Tracey KJ and Cerami A. Tumor necrosis factor: a pleiotropic cytokine and therapeutic target. *Annu Rev Med* 45: 491-503 (1994).
- [72] Suzumura A, Sawada M, Yamamoto H and Marunouchi T. Transforming growth factor-beta suppresses activation and proliferation of microglia *in vitro*. *J Immunol* 151(4): 2150-2158 (1993).
- [73] Rosen DR, Siddique T, Patterson D, Figlewicz DA, Sapp P, Hentati A, *et al.* Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. *Nature* 362(6415): 59-62 (1993).
- [74] Majoor-Krakauer D, Willems PJ and Hofman A. Genetic epidemiology of amyotrophic lateral sclerosis. *Clin Genet* 63(2): 83-101 (2003).
- [75] Yang Y, Hentati A, Deng HX, Dabbagh O, Sasaki T, Hirano M, *et al.* The gene encoding alsin, a protein with three guanine-nucleotide exchange factor domains, is mutated in a form of recessive amyotrophic lateral sclerosis. *Nat Genet* 29(2): 160-165 (2001).
- [76] Puls I, Jonnakuty C, LaMonte BH, Holzbaur EL, Tokito M, Mann E, *et al.* Mutant dynactin in motor neuron disease. *Nat Genet* 33(4): 455-456 (2003).
- [77] Chen YZ, Bennett CL, Huynh HM, Blair IP, Puls I, Irobi J, *et al.* DNA/RNA helicase gene mutations in a form of juvenile amyotrophic lateral sclerosis (ALS4). *Am J Hum Genet* 74(6): 1128-1135 (2004).
- [78] Hosler BA, Siddique T, Sapp PC, Sailor W, Huang MC, Hossain A, *et al.* Linkage of familial amyotrophic lateral sclerosis with frontotemporal dementia to chromosome 9q21-q22. *JAMA* 284(13): 1664-1669 (2004).
- [79] Tanaka M, Kikuchi H, Ishizu T, Minohara M, Osoegawa M, Motomura K, *et al.* Intrathecal upregulation of granulocyte colony stimulating factor and its neuroprotective actions on motor neurons in amyotrophic lateral sclerosis. *J Neuropathol Exp Neurol* 65(8): 816-25 (2006).
- [80] Kawamata T, Akiyama H, Yamada T and McGeer PL. Immunologic reactions in amyotrophic lateral sclerosis brain and spinal cord tissue. *Am J Pathol* 140(3): 691-707 (1992).
- [81] Henkel JS, Engelhardt JI, Siklos L, Simpson EP, Kim SH, Pan T, *et al.* Presence of dendritic cells, MCP-1, and activated microglia/macrophages in amyotrophic lateral sclerosis spinal cord tissue. *Ann Neurol* 55(2): 221-235 (2004).
- [82] Wilms H, Sievers J, Dengler R, Bufler J, Deuschl G and Lucius R. Intrathecal synthesis of monocyte chemoattractant protein-1 (MCP-1) in amyotrophic lateral sclerosis: further evidence for microglial activation in neurodegeneration. *J Neuroimmunol* 144(1-2): 139-142 (2003).
- [83] Baron P, Bussini S, Cardin V, Corbo M, Conti G, Galimberti D, *et al.* Production of monocyte chemoattractant protein-1 in amyotrophic lateral sclerosis. *Muscle Nerve* 32: 541-544 (2005).
- [84] Sekizawa T, Openshaw H, Ohbo K, Sugamura K, Itoyama Y and Niland JC. Cerebrospinal fluid interleukin 6 in amyotrophic lateral sclerosis: immunological parameter and comparison with inflammatory and non-inflammatory central nervous system diseases. *J Neurol Sci* 154(2): 194-199 (1998).
- [85] Poloni M, Facchetti D, Mai R, Micheli A, Agnoletti L, Francolini G, *et al.* Circulating levels of tumour necrosis factor-alpha and its soluble receptors are increased in the blood of patients with amyotrophic lateral sclerosis. *Neurosci Lett* 287(3): 211-214 (2000).
- [86] Ilzecka J, Stelmasiak Z and Dobosz B. Transforming growth factor-Beta 1 (TGF-Beta 1) in patients with amyotrophic lateral sclerosis. *Cytokine* 20(5): 239-243 (2002).
- [87] Bertram L and Tanzi RE. The genetic epidemiology of neurodegenerative disease. *J Clin Invest* 115(6): 1449-1157 (2005).
- [88] Kwon JM and Goate AM. The candidate gene approach. *Alcohol Res Health* 24(3): 164-168 (2000).

- [89] Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, *et al.* Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 261(5123): 921-923 (1993).
- [90] Pericak-Vance MA, Bebout JL, Gaskell PC Jr, Yamaoka LH, Hung WY, Alberts MJ, *et al.* Linkage studies in familial Alzheimer disease: evidence for chromosome 19 linkage. *Am J Hum Genet* 48(6): 1034-1050 (1991).
- [91] Raber J, Huang Y and Ashford JW. ApoE genotype accounts for the vast majority of AD risk and AD pathology. *Neurobiol Aging* 25(5): 641-650 (2004).
- [92] Poli M, Gatta LB, Lovati C, Mariani C, Galimberti D, Scarpini E, *et al.* Interaction between the APOE varepsilon4 allele and the APH-1b c+651T>G SNP in Alzheimer's disease. *Neurobiol Aging* 2007 Apr 25; [Epub ahead of print].
- [93] Grupe A, Li Y, Rowland C, Nowotny P, Hinrichs AL, Smemo S, *et al.* A scan of chromosome 10 identifies a novel locus showing strong association with late-onset Alzheimer disease. *Am J Hum Genet*; 78(1): 78-88 (2006).
- [94] Li Y, Grupe A, Rowland C, Nowotny P, Kauwe JS, Smemo S, *et al.* DAPK1 variants are associated with Alzheimer's disease and allele-specific expression. *Hum Mol Genet* 15(17): 2560-2568 (2006).
- [95] Du Y, Dodel RC, Eastwood BJ, Bales KR, Gao F, Lohmüller F, *et al.* Association of an interleukin 1 alpha polymorphism with Alzheimer's disease. *Neurology* 55(4): 480-483 (2000).
- [96] Grimaldi LM, Casadei VM, Ferri C, Veglia F, Licastro F, Annoni G, *et al.* Association of early-onset Alzheimer's disease with an interleukin-1alpha gene polymorphism. *Ann Neurol* 47(3): 361-365 (2000).
- [97] Nicoll JA, Mrak RE, Graham DI, Stewart J, Wilcock G, MacGowan S, *et al.* Association of interleukin-1 gene polymorphisms with Alzheimer's disease. *Ann Neurol* 47(3): 365-368 (2000).
- [98] Papassotiropoulos A, Bagli M, Jessen F, Bayer TA, Maier W, Rao ML, *et al.* A genetic variation of the inflammatory cytokine interleukin-6 delays the initial onset and reduces the risk for sporadic Alzheimer's disease. *Ann Neurol* 45(5): 666-668 (1999).
- [99] Licastro F and Chiappelli M. Brain immune responses cognitive decline and dementia: relationship with phenotype expression and genetic background. *Mech Ageing Dev* 124: 539-548 (2003).
- [100] Collins JS, Perry RT, Watson B Jr, Harrell LE, Acton RT, Blacker D, *et al.* Association of a haplotype for tumor necrosis factor in siblings with late-onset Alzheimer disease: the NIMH Alzheimer Disease Genetics Initiative. *Am J Med Genet* 96(6): 823-830 (2000).
- [101] Blacker D, Wilcox MA, Laird NM, Rodes L, Horvath SM, Go RC, *et al.* Alpha-2 macroglobulin is genetically associated with Alzheimer disease. *Nat Genet* 19(4): 357-360 (1998).
- [102] Huerta C, Alvarez V, Mata IF, Coto E, Ribacoba R, Martinez C, *et al.* Chemokines (RANTES and MCP-1) and chemokine-receptors (CCR2 and CCR5) gene polymorphisms in Alzheimer's and Parkinson's disease. *Neurosci Lett* 370(2-3): 151-154 (2004).
- [103] Combarros O, Infante J, Llorca J and Berciano J. No evidence for association of the monocyte chemoattractant protein-1 (-2518) gene polymorphism and Alzheimer's disease. *Neurosci Lett* 360(1-2): 25-28 (2004).
- [104] Fenoglio C, Galimberti D, Lovati C, Guidi I, Gatti A, Fogliarino S, *et al.* MCP-1 in Alzheimer's disease patients: A-2518G polymorphism and serum levels. *Neurobiol Aging* 25(9): 1169-1173 (2004).
- [105] Galimberti D, Fenoglio C, Lovati C, Gatti A, Guidi I, Venturelli E, *et al.* CCR2-64I polymorphism and CCR5Delta32 deletion in patients with Alzheimer's disease. *J Neurol Sci* 225(1-2): 79-83 (2004).
- [106] Combarros O, Infante J, Llorca J, Pena N, Fernandez-Viadero C and Berciano J. The chemokine receptor CCR5-Delta32 gene mutation is not protective against Alzheimer's disease. *Neurosci Lett* 366(3): 312-314 (2004).
- [107] Venturelli E, Galimberti D, Fenoglio C, Lovati C, Finazzi D, Guidi I, *et al.* Candidate gene analysis of IP-10 gene in patients with Alzheimer's disease. *Neurosci Lett* 404(1-2): 217-221 (2006).
- [108] Venturelli E, Galimberti D, Lovati C, Fenoglio C, Scalabrini D, Mariani C, *et al.* The T-786C NOS3 polymorphism in Alzheimer's disease: association and influence on gene expression. *Neurosci Lett* 382(3): 300-303 (2005).
- [109] Dahiyat M, Cumming A, Harrington C, Wischik C, Xuereb J, Corrigan F, *et al.* Association between Alzheimer's disease and the NOS3 gene. *Ann Neurol* 46(4): 664-667 (1999).
- [110] Crawford F, Freeman M, Abdullah L, Schinka J, Gold M, Duara R and Mullan M. No association between the NOS3 codon 298 polymorphism and Alzheimer's disease in a sample from the United States. *Ann Neurol* 47(5): 687 (2000).
- [111] Sanchez-Guerra M, Combarros O, Alvarez-Arcaya A, Mateo I, Berciano J, Gonzalez-Garcia J, *et al.* The Glu298Asp polymorphism in the NOS3 gene is not associated with sporadic Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 70: 566-567 (2001).
- [112] Tedde A, Nacmias B, Cellini E, Bagnoli S and Sorbi S. Lack of association between NOS3 polymorphism and Italian sporadic and familial Alzheimer's disease. *J Neurol* 249: 110-111 (2002).
- [113] Monastero R, Cefalu AB, Camarda C, Buglino CM, Mannino M, Barbagallo CM, *et al.* No association between Glu298Asp endothelial nitric oxide synthase polymorphism and Italian sporadic Alzheimer's disease. *Neurosci Lett* 341: 229-232 (2003).
- [114] Guidi I, Galimberti D, Venturelli E, Lovati C, Del Bo R, Fenoglio C, *et al.* Influence of the Glu298Asp polymorphism of NOS3 on age at onset and homocysteine levels in AD patients. *Neurobiol Aging* 26(6): 789-794 (2005).
- [115] Brown KS, Kluijtmans LA, Young IS, Woodside J, Yarnell JW, McMaster D, *et al.* Genetic evidence that nitric oxide modulates homocysteine: the NOS3 894TT genotype is a risk factor for hyperhomocystenemia. *Arterioscler Thromb Vasc Biol* 23(6): 1014-1020 (2003).
- [116] Galimberti D, Venturelli E, Gatti A, Lovati C, Fenoglio C, Mariani C, *et al.* Association of neuronal nitric oxide synthase C276T polymorphism with Alzheimer's disease. *J Neurol* 252: 985-986 (2005).
- [117] Liou YJ, Hong CJ, Liu HC, Liu CY, Liu TY, Chen IC, *et al.* No association between the neuronal nitric oxide synthase gene polymorphism and Alzheimer's disease. *Am J Med Gen* 114: 687-688 (2002).
- [118] Galimberti D, Scarpini E, Venturelli E, Strobel A, Herterich S, Fenoglio C, *et al.* Association of a NOS1 promoter repeat with Alzheimer's disease. *Neurobiol Aging* 2007 Apr 5; [Epub ahead of print].
- [119] Wang Y, Newton DC, Robb GB, Kau CL, Miller TL, Cheung AH, *et al.* RNA diversity has profound effects on the translation of neuronal nitric oxide synthase. *Proc Natl Acad Sci USA* 96(21): 12150-12155 (1999).
- [120] Saur D, Vanderwinden JM, Seidler B, Schmid RM, De Laet MH and Allescher HD. Single-nucleotide promoter polymorphism alters transcription of neuronal nitric oxide synthase exon 1c in infantile hypertrophic pyloric stenosis. *Proc Natl Acad Sci* 101(6): 1662-1667 (2004).
- [121] Reif A, Herterich S, Strobel A, Ehlis AC, Saur D, Jacob CP, *et al.* A neuronal nitric oxide synthase (NOS-I) haplotype associated with schizophrenia modifies prefrontal cortex function. *Mol Psychiatry* 11(3): 286-300 (2006).
- [122] Farrer LA, Abraham CR, Volicer L, Foley EJ, Kowall NW, McKee AC, *et al.* Allele epsilon 4 of apolipoprotein E shows a dose effect on age at onset of Pick disease. *Exp Neurol* 136: 162-170 (1995).
- [123] Gustafson L, Abrahamson M, Grubb A, Nilsson K and Fex G. Apolipoprotein-E genotyping in Alzheimer's disease and frontotemporal dementia. *Dement Geriatr Cogn Disord* 8: 240-243 (1997).
- [124] Helisalmi S, Linnaranta K, Lehtovirta M, Mannermaa A, Heinonen O, Ryyanen M, *et al.* Apolipoprotein E polymorphism in patients with different neurodegenerative disorders. *Neurosci Lett* 205: 61-64 (1996).
- [125] Stevens M, van Duijn CM, de Knijff P, van Broeckhoven C, Heutink P, Oostra BA, *et al.* Apolipoprotein E gene and sporadic frontal lobe dementia. *Neurology* 48: 1526-1529 (1997).
- [126] Fabre SF, Forsell C, Viitanen M, Sjögren M, Wallin A, Blennow K, *et al.* Clinic-based cases with frontotemporal dementia show increased cerebrospinal fluid tau and high apolipoprotein E epsilon4 frequency, but no tau gene mutations. *Exp Neurol* 168: 413-418 (2001).

- [127] Bernardi L, Maletta RG, Tomaino C, Smirne N, Di Natale M, Perri M, *et al.* The effects of APOE and tau gene variability on risk of frontotemporal dementia. *Neurobiol Aging* 27(5): 702-709 (2006).
- [128] Geschwind D, Karrim J, Nelson SF and Miller B. The apolipoprotein E epsilon4 allele is not a significant risk factor for frontotemporal dementia. *Ann Neurol* 44: 134-138 (1998).
- [129] Short RA, Graff-Radford NR, Adamson J, Baker M and Hutton M. Differences in tau and apolipoprotein E polymorphism frequencies in sporadic frontotemporal lobar degeneration syndromes. *Arch Neurol* 59: 611-615 (2002).
- [130] Riemenschneider M, Diehl J, Muller U, Forstl H and Kurz A. Apolipoprotein E polymorphism in German patients with frontotemporal degeneration. *J Neurol Neurosurg Psychiatry* 72: 639-641 (2002).
- [131] Srinivasan R, Davidson Y, Gibbons L, Payton A, Richardson AM, Varma A, *et al.* The apolipoprotein E epsilon4 allele selectively increases the risk of frontotemporal lobar degeneration in males. *J Neurol Neurosurg Psychiatry* 77: 154-158 (2006).
- [132] Engelborghs S, Dermaut B, Goeman J, Saerens J, Marien P, Pickut BA, *et al.* Prospective Belgian study of neurodegenerative and vascular dementia: APOE genotype effects. *J Neurol Neurosurg Psychiatry* 74: 1148-1151 (2003).
- [133] Verpillat P, Camuzat A, Hannequin D, Thomas-Anterion C, Puel M, Belliard S, *et al.* Apolipoprotein E gene in frontotemporal dementia: an association study and meta-analysis. *Eur J Hum Genet* 10: 399-405 (2002).
- [134] Baker M, Litvan I, Houlden H, Adamson J, Dickson D, Perez-Tur J, *et al.* Association of an extended haplotype in the tau gene with progressive supranuclear palsy. *Hum Mol Genet* 8(4): 711-715 (1999).
- [135] Di Maria E, Tabaton M, Vigo T, Abbruzzese G, Bellone E, Donati C, *et al.* Corticobasal degeneration shares a common genetic background with progressive supranuclear palsy. *Ann Neurol* 47(3): 374-377 (2000).
- [136] Houlden H, Baker M, Morris HR, MacDonald N, Pickering-Brown S, Adamson J, *et al.* Corticobasal degeneration and progressive supranuclear palsy share a common tau haplotype. *Neurology* 56: 1702-1706 (2001).
- [137] Ingelsson M, Fabre SF, Lilius L, Andersen C, Viitanen M, Almkvist O, *et al.* Increased risk for frontotemporal dementia through interaction between tau polymorphisms and apolipoprotein E epsilon4. *Neuroreport* 12: 905-909 (2001).
- [138] Pastor P, Ezquerria M, Tolosa E, Munoz E, Marti MJ, Valldeoriola F, *et al.* Further extension of the H1 haplotype associated with progressive supranuclear palsy. *Mov Disord* 17: 550-556 (2002).
- [139] Verpillat P, Camuzat A, Hannequin D, Thomas-Anterion C, Puel M, Belliard S, *et al.* Association between the extended tau haplotype and frontotemporal dementia. *Arch Neurol* 59: 935-939 (2002).
- [140] Goate A, Chartier-Harlin MC, Mullan M, Brown J, Crawford F, Fidani L, *et al.* Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature* 349(6311): 704-706 (1991).
- [141] Sherrington R, Rogaev EI, Liang Y, Rogaeva EA, Levesque G, Ikeda M, *et al.* Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. *Nature* 375(6534): 754-760 (1995).
- [142] Levy-Lahad E, Wasco W, Poorkaj P, Romano DM, Oshima J, Pettingell WH, *et al.* Candidate gene for the chromosome 1 familial Alzheimer's disease locus. *Science* 269(5226): 973-977 (1995).
- [143] Dermaut B, Kumar-Singh S, Engelborghs S, Theuns J, Rademakers R, Saerens J, *et al.* A novel presenilin 1 mutation associated with Pick's disease but not beta-amyloid plaques. *Ann Neurol* 55(5): 617-626 (2004).
- [144] Hadano S, Hand CK, Osuga H, Yanagisawa Y, Otomo A, Devon RS, *et al.* A gene encoding a putative GTPase regulator is mutated in familial amyotrophic lateral sclerosis 2. *Nat Genet* 29(2): 166-173 (2001).
- [145] Hand CK and Rouleau GA. Familial amyotrophic lateral sclerosis. *Muscle Nerve* 25(2): 135-59 (2002).
- [146] Hentati A, Ouahchi K, Pericak-Vance MA, Nijhawan D, Ahmad A, Yang Y, *et al.* Linkage of a commoner form of recessive amyotrophic lateral sclerosis to chromosome 15q15-q22 markers. *Neurogenetics* 2(1): 55-60 (1998).
- [147] Abalkhail H, Mitchell J, Habgood J, Orrell R and de Bellerocche J. A new familial amyotrophic lateral sclerosis locus on chromosome 16q12.1-16q12.2. *Am J Hum Genet* 73(2): 383-389 (2003).
- [148] Sapp PC, Hosler BA, McKenna-Yasek D, Chin W, Gann A, Genise H, *et al.* Identification of two novel loci for dominantly inherited familial amyotrophic lateral sclerosis. *Am J Hum Genet* 73(2): 397-403 (2003).
- [149] Nishimura AL, Mitne-Neto M, Silva HC, Richieri-Costa A, Middleton S, Cascio D, *et al.* A mutation in the vesicle-trafficking protein VAPB causes late-onset spinal muscular atrophy and amyotrophic lateral sclerosis. *Am J Hum Genet* 75(5): 822-831 (2004).
- [150] Clark LN, Poorkaj P, Wszolek Z, Geschwind DH, Nasreddine ZS, Miller B, *et al.* Pathogenic implications of mutations in the tau gene in pallido-ponto-nigral degeneration and related neurodegenerative disorders linked to chromosome 17. *Proc Natl Acad Sci USA* 95(22): 13103-13107 (1998).
- [151] Al-Chalabi A, Andersen PM, Nilsson P, Chioza B, Andersson JL, Russ C, *et al.* Deletions of the heavy neurofilament subunit tail in amyotrophic lateral sclerosis. *Hum Mol Genet* 8(2): 157-164 (1999).
- [152] Lambrechts D, Storkebaum E, Morimoto M, Del-Favero J, Desmet F, Marklund SL, *et al.* VEGF is a modifier of amyotrophic lateral sclerosis in mice and humans and protects motoneurons against ischemic death. *Nat Genet* 34(4): 383-394 (2003).
- [153] Corcia P, Khoris J, Couratier P, Mayeux-Portas V, Bieth E, De Toffol B, *et al.* SMN1 gene study in three families in which ALS and spinal muscular atrophy co-exist. *Neurology* 59(9): 1464-1466 (2002).
- [154] Veldink JH, van den Berg LH, Cobben JM, Stulp RP, De Jong JM, Vogels OJ, *et al.* Homozygous deletion of the survival motor neuron 2 gene is a prognostic factor in sporadic ALS. *Neurology* 56(6): 749-152 (2001).
- [155] Drory VE, Birnbaum M, Korczyn AD and Chapman J. Association of APOE epsilon4 allele with survival in amyotrophic lateral sclerosis. *J Neurol Sci* 190(1-2): 17-20 (2001).
- [156] Rothstein JD, Van Kammen M, Levey AI, Martin LJ and Kuncel RW. Selective loss of glial glutamate transporter GLT-1 in amyotrophic lateral sclerosis. *Ann Neurol* 38(1): 73-84 (1995).
- [157] Kawahara Y, Ito K, Sun H, Aizawa H, Kanazawa I and Kwak S. Glutamate receptors: RNA editing and death of motor neurons. *Nature* 427(6977): 801 (2004).