### Review



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Alzheimer's disease is the most common neurodegenerative disease and the cause of dementia. Although the pathomechanisms underlying Alzheimer's disease have not been fully elucidated, there is evidence that genetic and environmental factors contribute to its development. Immune system changes, both environmentally-induced and, as a result of predisposing genetics, are implicated in Alzheimer's disease etiopathogenesis. Genes associated with immune system dysfunction in Alzheimer's disease include CLU, BIN1, CR1, ABCA7, HLA-DRB1, TREM2, EPHA1, and CD2AP. In particular, BIN1 and CLU, aberrations in which are thought to promote neurodegeneration by dysregulating exocytosis and immune processes, together with the E4 variant of the APOE gene, are among the most common genetic risk factors for Alzheimer's disease. While the relationships between these genes in Alzheimer's disease have been examined, little information exists regarding their role as variables predisposing first or second-degree relatives of Alzheimer's disease patients to the illness. The rationale of this review is to suggest that individuals with a family history of Alzheimer's disease who have the BIN1-T/T variant may be at significant risk of developing Alzheimer's disease. Also, the unfavorable BIN1-T variant is independent of APOE E4associated risk. People at risk of developing Alzheimer's disease are more often carriers of the protective C-variant of the CLU gene, the presence of which might be associated with later-onset dementia observable within this highrisk group. It seems BIN1 and CLU together with, albeit independent of APOE E4, may be among the factors predisposing individuals with a family history of Alzheimer's disease to developing the illness.

### Keywords

Genetic variants; immune risk factors; Alzheimer's disease; immunopathology

## 1. Introduction

Alzheimer's disease (AD) is the most common form of irreversible and progressive dementia in the elderly and accounts for 50% of all types of dementia. It is characterized by gradual memory loss and cognitive impairment. Two AD subtypes differ in their pattern of inheritance: the familial form (FAD), which affects less than 1-5% of patients and is usually inherited in an autosomal dominant manner, and the more common sporadic form (SAD, 95-99%) which has a multifactorial background. AD may appear at different ages, but most patients develop late-onset AD (LOAD), which manifests after 60 years of age. Early-onset AD (EOAD) can also occur and is usually hereditary (Blennow et al., 2006; Dorszewska et al., 2016).

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The exact cause of AD is not fully known. While the etiology of AD is thought to be multifaceted, two conjectures dominate in attempting to explain what triggers pathogenesis of the disease: the A $\beta$  and  $\tau$  hyperphosphorylation hypotheses. The first posits that fibrils derived from the membrane-spanning domain of the type 1 glycoprotein, APP, by cleavage via  $\gamma$ -secretase accumulate extracellularly to form insoluble amyloid plaques, which prove neurotoxic by various mechanisms. The second suggests that  $\tau$ , an intrinsically disordered microtubule-associated protein (MAP), becomes hyperphosphorylated and forms neurofibrillary tangles (NFTs), which interfere with anterograde axonal transport and normal synaptic functions (Barbier et al., 2019). In 2018, the National Institute on Aging and the Alzheimer's Association (NIA-AA) designated markers that allow for a straightforward diagnosis of AD. These biomarkers include reduced  $A\beta$  concentration and increased level of hyperphosphorylated  $\tau$  protein in cerebrospinal fluid (CSF), together with the presence of  $A\beta$  and NFTs deposits in the brain, as detected by imaging modalities such as positron emission tomography (PET) (Jack et al., 2018).

Genetic and environmental factors both contribute to AD pathogenesis (Dorszewska et al., 2016; Kowalska et al., 2020). Environmental factors include diabetes, hypertension, smoking, obesity and dyslipidemia, brain injuries, cerebrovascular disease, and other vasculopathies, and a family history of dementia (Barba et al., 2000; Khan et al., 2019; Mayeux and Stern, 2012; Rastas et al., 2010; Tapiainen et al., 2020; Whitmer et al., 2005; Yu et al., 2020; Zhou et al., 2020). Among genetic factors, the apolipoprotein E (*APOE*) E4 variant is a significant risk factor for SAD and reduced recovery after brain injury. Pendlebury et al. (2020) showed that *APOE* E4 homozygosity was associated with dementia both be-

fore and after patients suffered from a transient ischemic attack or stroke. Moreover, it has been shown that the *APOE* E4 genotype and low plasma concentrations of apolipoprotein E (apoE) may be a risk factor for developing AD (Prendecki et al., 2016, 2019).

Prendecki et al. (2018) demonstrated that the most probable mechanistic explanation of neurodegeneration in AD patients bearing the *APOE* E4 variant involves oxidative stress, marked by *inter alia* increased homocysteine (Hcy) levels and reduced levels of 8-oxo-2'-deoxyguanosine (8-oxo2dG) and glutathione (GSH). Moreover, the studies of Prendecki et al. (2018, 2019) have shown that controls with a positive family history of AD did not have altered Hcy levels, but tended to have decreased levels of the natural antioxidant glutathione (GSH). In these individuals, changes in GSH level accompanied an increase in the concentration of the oxidative stress marker 8-oxo2dG and the enzyme responsible for its excision, 8-oxoguanine DNA glycosylase (OGG1). Imbalances in the levels of oxidative stress markers in individuals with a positive family history of AD may indicate mobilization of the body to counteract CNS oxidative stress.

Heneka et al. (2015) suggested that the pathogenesis of AD is not limited to neuronal disorders, but strongly relates to immune processes in the brain. That study pointed to the participation of astrocytes and microglia in AD development. These glia release chemical mediators of inflammation and are responsible for modulating immune responses. Moreover, in AD, both genetic factors associated with the immune system and external factors, including traumatic brain injury, obesity, and systemic inflammation, may disrupt neural-immune processes, thereby promoting the development of dementia.

The genes associated with inflammatory processes contributing to AD, neuropathology are *TREM2*, *CR1*, and *CD33* (Katsel and Haroutunian, 2019). It is currently believed that *BIN1* and *CLU* are also associated with AD pathogenesis. The role of the *BIN1* gene in the pathogenesis of AD has not yet been fully characterized (Han et al., 2019). However, the encoded protein is associated with intracellular A $\beta$  transport, immune responses, apoptosis, and endo/exocytosis of synaptic vesicles. Clusterin, the product of the *CLU* gene, also known as apolipoprotein J, is present in A $\beta$  plaques and binds to A $\beta$  peptides. Clusterin also plays an essential role in lipid transport, apoptosis, immune responses, and neurogenesis (Han et al., 2018).

Literature reports indicate that *BIN1* and *CLU* are associated with the pathogenesis of both FAD and SAD (Han et al., 2018, 2019). Importantly, *BIN1* and *CLU* are the second and third most common genetic risk factors for SAD after the *APOE* gene, respectively. All three of the said genes are associated with LOAD risk (Santos et al., 2020). To date, the correlation between these genes and AD has not been studied in the Polish population. It is also unknown whether the expression of these genes changes in individuals with a positive family history of AD, especially those with *APOE* E4 genotype.

## 2. Role of the immune system in the

pathogenesis of Alzheimer's disease.

In the last decade, data from preclinical and clinical studies have pointed to the immune system as having an integral role in the pathogenesis of AD. This so-called 'neuroinflammation hypothesis' emphasizes the dysregulation of CNS immune responses in AD, where both innate and adaptive pathways are involved (Ransohoff, 2016; Remarque et al., 2001). Still, it is contested whether immune responses predominantly contribute to the initiation and acceleration of AD or constitute a beneficial defense against neurotoxicity (Frost et al., 2019; Van Eldik et al., 2016).

It has been established that both extracellular, neuritic plaqueforming A $\beta$  deposits and misfolded, hyperphosphorylated  $\tau$  protein within NFTs generate a constant inflammatory environment, which activates microglia and astroglia (Edison et al., 2008; Shen et al., 2001; Vehmas et al., 2003). The recruitment of these glia provokes the alteration of the blood-brain barrier (BBB), increases blood vessel permeability, and may exacerbate neuronal damage. Recent data have identified neuroinflammatory processes resulting in BBB dysfunction as a critical component of AD (Cai et al., 2014; Carrano et al., 2012; Guerriero et al., 2017; Hansen et al., 2018; Takechi et al., 2017).

Microglia are the innate immune cells of the CNS and serve as resident phagocytes, thus playing a crucial role in tissue maintenance and defense against pathogens. They originate from erythromyeloid progenitor cells in the embryonic yolk sac, and after migration into the brain, spread throughout the parenchyma (Ginhoux et al., 2010). Microglia respond to local brain injury via a variety of surface receptors, many of which are expressed on cellular processes termed filipodia that contact neurons, astrocytes, and perivascular cells (Davalos et al., 2005; Hickman et al., 2018). Furthering research suggesting that microglia contribute mainly to the progression and escalation of AD, recent genome-wide association studies (GWAS) have established that the majority of genetic risk variants for LOAD are predominantly expressed in the innate immune system, e.g., APOE, TREM2, ABCA7, CD33, CR1 (Aikawa et al., 2019; Filipello et al., 2018; Fonseca et al., 2016; Griciuc et al., 2019; McQuade and Blurton-Jones, 2019; Vitek et al., 2009). These data are compatible with the hypothesis that microglia are also critically involved in the early steps of the disease (Heppner et al., 2015). Paradoxically, microglial A $\beta$  phagocytosis may contribute to increased A $\beta$  pathology by triggering the microglial release of inflammatory mediators such as cytokines, complement components, chemokines, and free radicals (Cai et al., 2014; Jorda et al., 2020). Specially, microglia have been implicated in neurodegeneration by activating cytosolic receptor NALP3 and lysosomal cathepsin-B, ultimately leading to the release of the key cytokine interleukin-1 $\beta$  (IL-1 $\beta$ ) (Halle et al., 2008). This interleukin is known to cause the secretion of nitric oxide (NO) and tumor necrosis factor  $\alpha$  (TNF)  $\alpha$ . It thus indirectly promotes the formation of  $A\beta$  plaques and neurodegeneration (Griffin et al., 1989). Also,  $\tau$  pathology contributes to neuroinflammation, however, here also, it is equivocal whether this process is mostly protective or damaging, as a result of conflicting data; likely, the consequences of  $\tau$ -induced neuroinflammation depend on the disease stage. It is also unclear whether altered microglial performance is an origin or consequence of  $\tau$  pathology insofar as deposits of this protein may trigger microglia to secrete factors leading to the posttranslational modification of  $\tau$  incipient to its aggregation (Ismail et al., 2020; Vogels et al., 2019).

The contribution of astrocytes to AD immunopathology is also noteworthy. These cells' contribution to AD pathology has been associated with increased cytokine production. It may involve nuclear factor kappa-light-chain-enhancer of activated B cells (NF $\kappa$ -B)-mediated release of complement protein C3 (Lian et al., 2015).

Furthermore, there is a growing recognition of complement system involvement in AD pathology. Studies have confirmed elevated concentrations of C3 and CR1 components in the cerebrospinal fluid of AD patients (Daborg et al., 2012). Moreover, complement pathway activation has been associated with synapse loss mediated by C3/CR3 in response to oligomeric A $\beta$  (Hong et al., 2016). Nonetheless, the data are conflicting as to whether complement interaction with A $\beta$  is protective or detrimental. Some studies have demonstrated that complement deficiency results in accelerated A $\beta$  pathology (Maier et al., 2008; Wyss-Coray et al., 2002). Alternately, the elimination and modulation of microglial CR3 decrease the A $\beta$  level (Czirr et al., 2017), and C3 antagonists counteract plaque accumulation (Lian et al., 2015).

Recent studies have evidenced that monocytes/macrophages, lymphocytes, and T cells increasingly infiltrate the brain in both AD animal models and humans, confirming that the contribution of the immune system to AD pathogenesis is not limited to the CNS (Busse et al., 2017; Gate et al., 2020; McManus et al., 2015; Saresella et al., 2010). In particular, various cytokines and chemokines secreted by microglia may allow CCR2+ (C-C chemokine receptor 2) mononuclear phagocytes to enter the brain (Cao and Zheng, 2018; Mildner et al., 2007). In murine AD models, neutrophils, which respond quickly post-infection to phagocytose microorganisms, have been shown to enter the brain through LFA1 integrin attachment and surround A $\beta$  plaques with neutrophil extracellular traps (NETs) thereby contributing to chronic neuroinflammation (Kolaczkowska and Kubes, 2013; Zenaro et al., 2015). Notably, recent research has evidenced that neurodegeneration may also be influenced by peripheral inflammatory conditions such as periodontitis, as mediated by microglial priming and the increased production of proinflammatory cytokines (Ide et al., 2016). Indeed, neuroinflammation has a complex role in AD pathology, the details of which have yet to be fully unraveled.

# 3. Immune system-associated genetic risk factors for Alzheimer's disease

The recent GWAS meta-analysis involving 94,437 clinically diagnosed LOAD patients performed by Kunkle et al. (2019) indicated new AD risk loci, including numerous genes associated with the immune system: *CLU, BIN1, CR1, ABCA7, HLA-DRB1, TREM2, EPHA1* and *CD2AP*. Previous meta-analyses also underlined the role of CD33 and MS4A4/MS4A6 (Naj et al., 2011) in increasing LOAD risk. Table 1. summarizes the results of metaanalyses focused on single nucleotide polymorphisms (SNPs) in the genes mentioned above.

*ABCA7* encodes the ATP-binding cassette transporter A7 (ABCA7), which is a member of the A subfamily of ABC transporters. It is highly expressed in the brain, especially in microglia, and known to be involved in transmembrane lipid transport. It stimulates the efflux of cholesterol and phospholipids to bound apolipoprotein A-I (apoA-I) and apoE. Recent studies have also evidenced that ABCA7 is required for microglial and macrophagal

phagocytic clearance of  $A\beta$ , a cellular role that reflects its neural expression profile (Aikawa et al., 2018; Iwamoto et al., 2006; Kim et al., 2006). According to mouse model studies, a lack of ABCA7 results in the doubling of  $A\beta$  accumulation without alterations to amyloid precursor protein (APP) processing and apoE concentration. This suggests that ABCA7 regulates  $A\beta$  homeostasis via phagocytosis rather than by modulating lipid metabolism (Kim et al., 2013). Steinberg et al. (2015) substantiated that the rare loss of function (LOF) variants in the *ABCA7* gene are associated with an increased risk of developing AD. Moreover, polymorphisms in *ABCA7* were associated with increased risk for LOAD, concomitant to work by Apostolova et al. (2018), which showed that a correlation exists between polymorphisms in *ABCA7* (rs3764650 and rs3752246) and amyloid deposition, whose strength is second only to that between *APOE4* variants and the said pathology.

A recent meta-analysis proposed that polymorphisms in the gene encoding CD2-associated protein (CD2AP) are an important genetic risk factor for LOAD (Lambert et al., 2013). However, little remains known about the role of CD2AP in AD etiopathogenesis. CD2AP is expressed in immune cells, endothelial cells, and neurons, and maintains the BBB (Cochran et al., 2015). The primary function of CD2AP is to bind CD2 and regulate the interaction between T lymphocytes and antigen-presenting cells (Dustin et al., 1998). Moreover, CD2AP can interact with cytoskeletal molecules and initiate numerous intracellular signal transduction pathways via its SH3 domains (Cummins et al., 2018). Interestingly, CD2AP was found to be expressed at lower levels in the peripheral lymphocytes of AD patients (Tao et al., 2019). LOF variants in *CD2AP* led to enhanced A $\beta$  production,  $\tau$ -induced neurotoxicity, and reduced BBB integrity (Tao et al., 2019).

Genetic variants in EPHA1, MS4A4, and CD33 are associated with LOAD risk. However, their exact role in AD is still unknown. EPHA1 encodes the ephrin type-A receptor 1 (EPHA1), which belongs to the ephrin receptor subfamily of the proteintyrosine kinase family. It is expressed by CD4-positive T lymphocytes and monocytes and plays a role in neuronal morphogenesis and synaptic plasticity (Karch and Goate, 2015; Martinez et al., 2005). Ephrin over- or under expression was found in cancer cell lines and implicated in tumor progression, malignancy, and prognosis (Ieguchi and Maru, 2019). The membrane-spanning 4A (MS4A) family (e.g., MS4A4A, MS4A4E, MS4A6E) proteins are expressed in myeloid cells and monocytes. They are structurally similar to CD20, and likely control the activation of B-cell antigen receptors by regulating calcium influx (Polyak et al., 2008; Zuccolo et al., 2010). CD33 belongs to the sialic acid-binding immunoglobulin (Ig)-like family and inhibits microglia and monocytes via immunoreceptor tyrosine-based inhibition motifs (Paul et al., 2000). It is involved in numerous cellular processes: phagocytosis, cytokine release inhibition, adhesion, immune cell growth, and apoptosis (Zhao, 2019). Elevated expression of CD33 in the brains of AD patients promotes microglial activation and inhibits microglial uptake of A $\beta$ , thereby reducing A $\beta$  clearance (Griciuc et al., 2013). CD33 knockout increased microglial activation and reduced A $\beta$  plaque deposition (Griciuc et al., 2019). Further, the minor allele (A) of the rs3865444 polymorphism (decreased expression of CD33) protects against LOAD. In contrast, the major allele (C) (risk allele, increased expression of CD33) contributes

| Gene   | Possible role in LOAD  | Variant     | Major/minor<br>alleles | MAF    | OR   | Meta-ana<br>95% CI | lysis<br>P            | Reference                  |
|--------|--|-------------|------------------------|--------|------|--------------------|-----------------------|----------------------------|
| CLU    | Immune system response,  | rs1532278   | C/T                    | 0.26   | 0.89 | 0.85-0.93          | $8.3 \times 10^{-8}$  | Naj et al. (2011)          |
|        | cholesterol metabolism,  | rs2279590   | C/T                    | 0.24   | 0.86 | 0.82-0.90          | $1.9\times10^{-12}$   | Zhang et al. (2015)        |
|        | $A\beta$ metabolism  | rs9331888   | C/G                    | 0.33   | 1.1  | 1.05-1.15          | < 0.001               | Shuai et al. (2015)        |
|        |  | rs11136000  | C/T                    | 0.38   | 0.86 | 0.84-0.89          | < 0.0001*             | Han et al. (2018)          |
|        |  | rs9331896   | T/C                    | 0.38   | 0.88 | 0.85-0.90          | $4.6 \times 10^{-24}$ | Kunkle et al. (2019)       |
| BIN1   | Synaptic dysfunction and   | rs7561528   | G/A                    | 0.2    | 1.17 | 1.13-1.22          | $4.2\times10^{-14}$   | Naj et al. (2011)          |
|        | cell membrane processes,   | rs12989701  | C/A                    | 0.09   | 1.2  | 1.12-1.29          | < 0.0001              | Dong et al. (2017)         |
|        | microglia transcriptome,   | rs744373    | A/G                    | 0.36   | 1.15 | 1.11-1.20          | < 0.01                | Almeida et al. (2018)      |
|        | immune system response   | rs6733839   | C/T                    | 0.4    | 1.2  | 1.17-1.23          | $2.1\times10^{-44}$   | Kunkle et al. (2019)       |
| ABCA7  | Immune system response,  | rs3764650   | T/G                    | 0.2    | 1.23 | 1.18-1.30          | $4.5 \times 10^{-17}$ | Hollingworth et al. (2011) |
|        | cholesterol metabolism,  | rs4147929   | G/A                    | 0.19   | 1.15 | 1.11-1.19          | $1.1\times10^{-15}$   | Lambert et al. (2013)      |
|        | $A\beta$ metabolism  | rs3752246   | C/G                    | 0.17   | 1.15 | 1.11-1.18          | $3.1\times10^{-16}$   | Kunkle et al. (2019)       |
| CD2AP  | Immune system response,  | rs10948363  | A/G                    | 0.19   | 1.1  | 1.07-1.13          | $5.2\times10^{-11}$   | Lambert et al. (2013)      |
|        | synaptic dysfunction and   | rs9349407   | G/C                    | 0.19   | 1.08 | 1.05-1.12          | $8.78 \times 10^{-7}$ | Chen et al. (2015)         |
|        | cell membrane processes  | rs9473117   | A/C                    | 0.19   | 1.09 | 1.06-1.12          | $1.2 \times 10^{-10}$ | Kunkle et al. (2019)       |
| EPHA1  | Immune system response,  | rs11767557  | T/C                    | 0.2    | 0.9  | 0.86-0.93          | $6.0 \times 10^{-10}$ | Hollingworth et al. (2011) |
|        | synaptic dysfunction and cell membrane processes                               | rs10808026  | C/A                    | 0.21   | 0.9  | 0.88-0.93          | $1.3 \times 10^{-10}$ | Kunkle et al. (2019)       |
| MS4A4A | Immune system response   | rs4938933   | T/C                    | 0.38   | 0.88 | 0.85-0.92          | $1.7 \times 10^{-9}$  | Naj et al. (2011)          |
| CD33   | Immune system response,<br>synaptic dysfunction and<br>cell membrane processes | rs3865444   | C/A                    | 0.21   | 0.92 | 0.89-0.95          | $3.61 \times 10^{-8}$ | Moreno-Grau et al. (2019)  |
| TREM2  | Immune system response   | rs143332484 | C/T                    | < 0.01 | 1.65 | 1.24-2.21          | 0.001                 | Lu et al. (2015)           |
|        |  | rs2234255   | G/A                    | < 0.01 | 3.65 | 1.61-8.28          | 0.002                 | Jiang et al. (2016)        |
|        |  | rs75932628  | C/T                    | < 0.01 | 2.08 | 1.73-2.49          | $2.7\times10^{-15}$   | Kunkle et al. (2019)       |
| CR1    | Immune system response   | rs3818361   | G/A                    | 0.25   | 1.18 | 1.13-1.24          | $3.7\times10^{-14}$   | Hollingworth et al. (2011) |
|        |  | rs6656401   | G/A                    | 0.07   | 1.14 | 1.08-1.20          | < 0.01                | Almeida et al. (2018)      |
|        |  | rs4844610   | C/A                    | 0.06   | 1.17 | 1.13-1.21          | $3.6\times10^{-24}$   | Kunkle et al. (2019)       |

Table 1. Results of a meta-analysis of immune-system associated genes and LOAD

LOAD - late-onset Alzheimer's disease; MAF - minor allele frequency, according to Ensembl database; OR - odds ratio; P - P-value in meta-analysis. \* only Caucasian population

to a more severe cognitive decline in AD, as represented by lower MMSE scores (Karch et al., 2012). Also, the *CD33* risk allele leads to a higher triggering receptor expressed on myeloid cells 2 (TREM2) expression (Chan et al., 2015). TREM2, encoded by the *TREM2* gene, is another microglial receptor. TREM2 activation stimulates phagocytosis and suppresses inflammation and thus induces microglial clearance of  $A\beta$ , in contrast to the effect of CD33 (Griciuc et al., 2019). Loss or underexpression of TREM2 reduces microglial activation and impairs microglia- $A\beta$  clustering, leading to increased  $A\beta$  plaque formation, increased autophagy, and dysfunction in energetic metabolism (Huang and Xu, 2019). AD mouse model studies showed that TREM2 is required for gene expression changes in 5xFAD; CD33-/-microglia, whereas differential gene expression in 5xFAD; TREM2-/- microglia did not depend on CD33. This suggests that TREM2 acts downstream of CD33 in modulating microglial pathology in AD. On the other hand, overexpression of TREM2 reprograms microglia and can reduce A $\beta$  plaques and memory deficits (Lee et al., 2018).

In their study analyzing microglia isolated from PS/APP transgenic mice, Krasemann et al. (2017) described a new 'neurodegenerative' microglial phenotype, termed MGnD, characterized *inter alia* by pronounced overexpression of apoE. Subsequently, the authors reported a positive correlation between *APOE* mRNA levels and the progression of neuropathology, such that it was abolished in the absence of TREM2. This suggests that  $A\beta$  activated microglia overproduce apoE in a TREM2 dependent manner. According to Parhizkar et al. (2019), the loss of functional TREM2 leads to reduced expression of apoE in microglia and reduced release of this apolipoprotein from microglia and/or astrocytes. Consequently, decreased apoE levels may be found in the A $\beta$  plaques of both *TREM2* knockout (KO) mice and human carriers of deleterious *TREM2* variants (p.R47H, p.R62C, p.R62H, and p.D87N).

Moreover, according to Yeh et al. (2016), TREM2 may directly interact with apoE as well as with CLU encoded apolipoprotein J (clusterin), the authors also reported the interaction to be impaired by AD linked TREM2 variants. Interestingly, while the TREM2 KO murine model was characterized by a significantly increased seeding of A $\beta$  plaques in the early stages of AD pathology, a reduction of  $A\beta$  burden and the formation of diffuse plaques was observed in advanced stages of the disease. Nonetheless, the accumulation of hippocampal A $\beta$  diffuse plaques and oligomers led to dendritic spine loss and axonal dystrophy in TREM2 deficient brains (Parhizkar et al., 2019). The TREM2 receptor may be essential for the early activation of microglia in response to newly seeded A $\beta$  plaques and oligomers. This process could facilitate LRP1 receptor-mediated amyloid clearance through the BBB (Ma et al., 2018). Together these results suggest that TREM2 may act as a neuroprotective agent in facilitating the removal of soluble  $A\beta$  (Meilandt et al., 2020). The role of TREM2 in AD may not be limited to immune response and  $A\beta$  turnover. Cruchaga et al. (2013) demonstrated that AD patients with the rs75932628-T risk allele had higher CSF  $\tau$  levels. Also, the rs75932628-T variant is associated with an increased risk of  $\tau$  dependent frontotemporal dementia, Parkinson's disease, and amyotrophic lateral sclerosis (Karch and Goate, 2015).

Another factor associated with aberrant immune function in AD is complement receptor type 1 (CR1), also known as the C3b/C4b receptor or CD35. The *CR1* gene encodes four protein isoforms. CR1 is mostly expressed on the surface of leukocytes and erythrocytes and binds to complement components, playing a vital role in the phagocytic removal of antibody-antigen immune complexes from the blood (Holers, 2014; Tuveson et al., 1991). Studies have shown that  $A\beta42$  can activate the complement system (Velazquez et al., 1997). Intelligibly, chronic activation of the complement system and inflammation occur throughout AD. Moreover, autopsy examinations of brain tissue from AD patients showed that CR1 expression correlates with advanced cognitive decline (Karch et al., 2012).

Deleterious *APOE* variants are recognized as the most significant risk factor for developing AD (Wadhwani et al., 2019). ApoE, like other apolipoproteins, is a cholesterol chaperone and a ligand for members of the low-density lipoprotein (LDLR) receptor family. It participates in the transport of cholesterol and is involved in the removal of toxic  $A\beta$  oligomers that are precursors to amyloid plaques. The *APOE* E4 isoform has been shown to have impaired ability to bind and remove  $A\beta$ , which results in reduced receptormediated uptake and cellular metabolism of the *APOE*/ $A\beta$  complex. In contrast, the *APOE* E2 isoform has the opposite effect (Arold et al., 2012). The E4 allele is much more common in people with AD than in the general population. The risk of developing AD depends on the number of E4 alleles, which can be zero, one, or two (Prendecki et al., 2019). Studies by Strittmatter et al. (1993), Saunders (2000), and Corder and Caskey (2009) have shown that patients with the E4/E4 genotype are 8 times more likely to develop AD than those with the E2/E3 or E3/E3 genotypes. A 2014 GWAS analysis confirmed that the E4 allele is an AD risk factor with an odds ratio (OR) of 2-5 (Chouraki and Seshadri, 2014). This data is in line with results from Prendecki et al. (2019) performed on 230 subjects: 88 AD patients, diagnosed according to NINCDS-ADRDRDA criteria (65.9% women, mean age 75.6 years), 62 persons with a positive family history of AD, i.e., first or second-degree relatives of AD patients (67.7% women, mean age 65.3 years), and 80 healthy persons without signs of dementia or other neurological disorders (78.8% women, mean age 71.6 years). The E4 allele occurred up to 3.6 times more often in persons with familial history of AD than in controls (P < 0.001, Fisher's exact test, FET). In contrast, the protective allele APOE E2 was more common in the control group. These results were reported in the literature (Corder and Caskey, 2009; Prendecki et al., 2019) and confirm that variants at the APOE locus partly contribute to the increased risk of developing AD in people with a family history of AD.

# 4. *BIN1* and *CLU* genes in people at risk of developing Alzheimer's disease

The presence of deleterious variants in *BIN1* and *CLU* may lead to excessive  $A\beta$  accumulation and ensuing immune dysfunction in AD (Ovsepian et al., 2018; Van Acker et al., 2019). Literature reports indicate that *BIN1* and *CLU* are associated with the pathogenesis of late-onset FAD and SAD (Marioni et al., 2018; Tanzi, 2012). In a recent association study performed by Santos et al. (2020), *BIN1* and *CLU* were shown to additively contribute to LOAD risk, together with *APOE*. Nonetheless, these two genes have not yet been adequately examined in the Polish population in the context of AD.

*BIN1* is the second most common genetic risk factor identified by GWAS for SAD after *APOE* (Lambert et al., 2013). Polymorphisms in this gene have also been found in patients with late-onset FAD (Wijsman et al., 2011). *BIN1* is located on the long arm of chromosome 2 at the 2q14.3 locus (Chouraki and Seshadri, 2014). One of the most interesting variants at the *BIN1* locus is rs6733839. GWAS have identified this common variant as a risk factor for AD, albeit with a modest odds ratio (OR = 1.22, CI = 1.18-1.25) (Chouraki and Seshadri, 2014). These data were confirmed by a subsequent study on genetic variants associated with the function of the BBB (Juul Rasmussen et al., 2019). Interestingly, the rs6733839 variant was connected with variations in neuroanatomical features such as the volume of the left inferior parietal lobule at baseline and, in a follow-up study, the right inferior parietal lobule (Li et al., 2017).

A part of The International Genomics of Alzheimer's Project (IGAP), the large GWAS meta-analysis published by Lambert et al. (2013), revealed that the T allele of the *BIN1* rs6733839 variant was a significant risk factor for AD. It has been demonstrated that persons with two copies of the T allele (T/T) at this locus achieved significantly worse results in episodic memory tests compared to individuals with other genotypes (C/T + C/C) (Greenbaum et al., 2016). According to McMillan et al. (2018), the rs6733839 minor variant was associated with an increased risk of developing AD based on PENN cohort data, as opposed to NACC cohort data.

The study of Dorszewska et al. (2019) performed on 126 subjects (40 AD patients, 47 persons with a positive family history of AD, as described above, and 39 control subjects) evidenced that the T/T genotype was more common in individuals related to AD patients as compared to control and AD groups (P < 0.001, Chi-squared test). Concomitantly, the C/T genotype was most common in the control group, in line with the above literature. Indeed, individuals with a positive family history of AD who possess the BIN1-T/T variant may be at a pronounced risk of developing AD in the future. Our previously mentioned results also evidenced that the unfavorable BIN1-T/T variant occurred significantly more often in individuals related to those suffering from AD, who were not carriers of the APOE E4 allele (P < 0.001, FET), indicating that T/T homozygote carriers are at greater risk of developing a cognitive disorder even if they are negative for the said apolipoprotein variant (Dorszewska et al., 2019).

While the discussed genetic variants of BIN1 are connected to AD pathology, the corresponding pathways that promote AD have not been fully elucidated and remain the subject of extensive study (Giri et al., 2016). It is known that BIN1 encodes the bridge integrator 1 (BIN1) protein, which is associated with immune responses, apoptosis, clathrin-mediated synaptic vesicle exocytosis (De Rossi et al., 2017) and likely synaptic function and memory consolidation (De Rossi et al., 2020). It is believed that BIN1 is associated with the intracellular transport of APP and  $A\beta$ via regulation of  $\beta$ -site cleaving enzyme 1, encoded by *BACE1* (Miyagawa et al., 2016). Moreover, the loss of BIN1 was shown to promote age-related inflammation and cancer susceptibility in transgenic mice (Chang et al., 2007). These data are in line with the in vitro study of autopsy brains harvested from transgenic mice lacking neuronal murine Bin1 and expressing mutated  $\tau$  P301S (McAvoy et al., 2019). The authors showed reduced excitability in isolated primary neurons accompanied by significant changes of microglia transcriptome of analyzed animals. The harvested microglia showed marked activation of various canonical pathways associated with, e.g., ROS and NOS production by macrophages as well as enhanced neuroinflammation signaling. In contrast, APP, as well as inflammation associated lipopolysaccharide (LPS) and interferon- $\gamma$ , were predicted as upstream activators. Interestingly, the observed changes were not present in control mice expressing  $\tau$  P301S and normal Bin1. These data suggest the participation of BIN1 in AD pathology may not be limited to  $A\beta$  turnover and disturbed inflammatory response. Chapuis et al. (2013) stipulated that elevated BIN1 expression increases the risk of AD by promoting  $\tau$  hyperphosphorylation, however, due to the small size of the study group, definite conclusions could not be drawn. Similarly, Crotti et al. (2019) demonstrated that vesicles containing BIN1 isolated from the cerebrospinal fluid of AD patients might contain  $\tau$  protein and facilitate  $\tau$  seeding. The authors also found that BIN1 overexpression may enhance the extracellular vesiclemediated spreading of  $\tau$ . Therefore, it seems that *BIN1* may participate in the development of  $\tau$  pathology leading to AD. Nonetheless, other studies have shown that BIN1 polymorphisms are associated with a reduced risk of developing primary age-related tauopathy (McMillan et al., 2018). Indeed, inconsistencies exist in the data obtained thus far regarding the role of BIN1 in AD pathogenesis, warranting continued research.

A $\beta$  transport out of the brain, as well as A $\beta$  fibrillization, are also regulated by the protein clusterin (Tanzi, 2012). This protein is encoded by the CLU gene, which is located on the short arm of chromosome 8 at the 8p21.1 locus. GWAS have identified CLU as the third most crucial locus associated with SAD (Tanzi, 2012; Vishnu et al., 2016). Also, it is believed to be involved in the pathogenesis of late-onset FAD (Jansen et al., 2019). One of the most interesting polymorphisms in CLU locus is rs9331896. According to GWAS, the major allele (C) has been identified as a protective factor, modestly reducing the risk of AD (OR = 0.86; CI = 0.84-0.89) (Chouraki and Seshadri, 2014). These results are in line with a newer study, performed on 362, 338 Danish individuals (Nordestgaard et al., 2018). According to Lambert et al. (2013), the C allele of the rs9331896 variant in CLU may be associated with a 16% reduction in the risk for AD. Similar results were obtained by Bressler et al. (2017). The latter showed that people with the C allele of the rs9331896 polymorphism obtained a higher result in the Delayed Word Recall Test (DWRT). Also, according to Rasmussen et al. (2019), the CLU-T allele of this polymorphism was associated with an elevated risk of developing AD. These data are in line with our work described above, where we determined that persons related in the first or second degree to AD patients were more often carriers of the protective C-variant of CLU rs9331896 polymorphism (P < 0.05, Chi-squared test). The presence of this protective variant of CLU may explain why some individuals in the high-risk group (the relatives of AD patients) do not develop symptoms of dementia. This protective effect may be particularly pronounced in persons who do not carry the pathological APOE E4 variant, as was found in our study (P < 0.05, FET) (Dorszewska et al., 2019).

The mechanism of the protective action of the CLU rs9331896 polymorphism remains unknown. However, this variant may lead to increased activity of CLU in affected individuals. It is known that clusterin is a versatile protein that may act as a chaperone for  $A\beta$  and regulate apoptosis, cholesterol transport, and inflammatory responses (Foster et al., 2019). Since clusterin has been identified as an effective silencer of the complement system by inhibition of the formation of the membrane attack complex (Kirszbaum et al., 1992), it has been hypothesized that clusterin may act as a regulatory element of aggregation associated inflammatory response in AD (Nuutinena et al., 2009). Clusterin may also act as a microglia activator, as described by Xie et al. (2005). The authors observed the increased production of reactive nitrogen species and TNF- $\alpha$  by rat microglia treated with exogenous human clusterin. This effect was persistent in microglia-neuronal in vitro co-cultures leading to neurotoxic effects.

Moreover, increased clusterin levels were found in acutely isolated 5xFAD transgenic murine microglia, that exhibited LPSlike induced protein profile by mass spectrum proteomic analysis (Rangaraju et al., 2018). As mentioned above, the clusterin ADassociated pathways may not be limited to immune response. It has been shown that clusterin binds reversibly to  $A\beta$  and affects its clearance (rate of amyloid removal) across the BBB (Wojtas et al., 2017). Clusterin levels increase under conditions of neuronal damage (Rasmussen et al., 2019). Accordingly, increased clusterin levels have been observed in AD in plasma (Weinstein et al., 2016) and brain areas affected by  $A\beta$  deposition, however, the measured clusterin increase was not sufficient to counteract increased A $\beta$  production (Miners et al., 2017). Moreover, it has been demonstrated that intravenous infusions of a clusterin-derived 10amino-acid peptide improved cognitive function and reduced A $\beta$ pathology in the 5x transgenic murine model of FAD (Qi et al., 2018). Therefore, clusterin seems to be a promising biomarker and possible target for future therapies directed to counteract A $\beta$ deposition.

# 5. A new look at the role of the immune system in the treatment of Alzheimer's disease

Already the foremost cause of dementia and the sixth leading cause of death in the world, the impact of AD on health care systems is expected to rise owing to increasing global life expectancies (Montanari et al., 2019). Even so, symptomatic treatment currently constitutes the only therapy for AD (Montanari et al., 2019). While experimental treatments for AD have been focused upon disturbing both pathogenic  $\tau$  and A $\beta$  protein aggregates, a stronger correlation has been found to exist between dementia and  $\tau$  hyperphosphorylation than amyloid deposition (Arriagada et al., 1992; Sigurdsson, 2008). Duly, various approaches have been exploited in the development of treatments for tauopathy in AD including the use of kinase inhibitors for impeding  $\tau$  hyperphosphorylation, enhancement of physiological processes involved in the clearance of damaged proteins, small-molecule inhibition of aggregate formation, pharmacologic stabilization of microtubules, proteolysis, and immunotherapy (Schroeder et al., 2015). The last of these has, over the last ten years, surfaced as a highly promising avenue for preventing AD pathology, as related to both A $\beta$  and  $\tau$  hyperphosphorylation (Schroeder et al., 2015).

Immunotherapy is either active or passive. In the former kind, antigens, typically combined with adjuvants, are injected into the cerebrospinal fluid and promote antibody production incipient to clearance of the antibody-pathologic protein complex by phagocytic cells of the host's innate immune system. Passive immunization involves the direct administration of exogenous antibodies. Since the seminal research (Kfoury et al., 2012), which evidenced prion-like trans-cellular transmission of  $\tau$ , immunotherapy aimed at reducing  $\tau$  aggregation has become a promising research objective (reviewed well by Schroeder et al. (2015)). The first active immunotherapy attempt involved administration of recombinant full-length human  $\tau$  with complete Freund's adjuvant (CFA) and pertussis toxin (PT) to wild type mice (Rosenmann et al., 2006). CFA and PT stimulate the proinflammatory Th1 response, promoting antigenic passage through the BBB. Intelligibly, these highly immunogenic adjuvants induced encephalomyelitis in the mice, a side-effect that was subsequently circumvented via the use of three phospho- $\tau$  peptides and AD mouse models ( $\tau$  E257T and P301S, where both mutations occur within the microtubule-binding region of the protein) (Boimel et al., 2010). Significant reductions were noted in NFTs as a result of the latter. Administration of the adjuvants alone promoted monocyte infiltration without the microglial activation, i.e., acquisition of the M1 pro-inflammatory phenotype (Rozenstein-Tsalkovich et al., 2013) that capacitates the phagocytic activity of these cells. Notably, it has been shown that impaired microglial phagocytic activity as a result of experimentally

ablated adaptive immune system cells, worsened neuroinflammation and A $\beta$  plaque deposition (Marsh et al., 2016). Another study using the  $\tau$  PHF1 epitope in combination with Freund's adjuvant in mice overexpressing the P301L mutation showed that older mice developed significantly increased astrocytosis and GFAP levels (Bi et al., 2011).

Interestingly, astrocyte-derived complement factor 3 (C3) and neuronal C1q promote microglial synaptic pruning and phagocytosis (Jevtic et al., 2017). Important progress in active immunotherapy was made when the Sigurdsson lab elegantly demonstrated that antibodies against  $\tau$  could cross the BBB of JNPL3 P301L mice to colocalize with NFTs, in contrast to those exogenously injected into nontransgenic mice, suggesting the barrier is compromised in tauopathies (Sigurdsson, 2009). Anti- $\tau$  antibodies, generated either by the host's immune system as a result of active immunotherapy, or delivered exogenously as a result of passive immunotherapy might promote clearance of pathological  $\tau$  aggregates by different mechanisms including neuronal uptake and subsequent lysosomal degradation, impairment of antibody-antigen uptake preventing trans-cellular transmission, or microglial phagocytosis (Schroeder et al., 2015). Importantly, however, recent research suggests that oligomeric forms of both au(Hill et al., 2019) and A $\beta$  (Dionisio-Santos et al., 2019) are more neurotoxic than NFTs and amyloid plaques, respectively, ratifying the need for early detection of AD pathology and prompt therapeutic intervention after that.

Microglia are critical modulators of neuroinflammation in AD. Increased levels of pro-inflammatory cytokines, including IL-1 $\beta$ , IL-6, IL-12, IL-12, IL-18, and TNF, have been shown to occur in the CSF of AD patients, possibly as a result of TL4/CD14mediated microglial interaction with  $A\beta$  (Dionisio-Santos et al., 2019). Promoting the M1 microglial state, these cytokines are thought to trigger a reduction in amyloid plaque burden, albeit at the cost of increasing hyperphosphorylated  $\tau$  species (Dionisio-Santos et al., 2019). Importantly, the generation of specific proinflammatory cytokines, e.g., IL-1 $\beta$  and IL-18 depends on the activity of the microglial inflammasome, which, activated by fibrillar A $\beta$  binding to Nod-like receptor protein 3 (NLRP3), has recently been highlighted as a potential therapeutic target in AD and other neurodegenerative conditions (Deora et al., 2020; Dionisio-Santos et al., 2019). The microglial-ApoE-triggering receptor expressed on myeloid cells 2 (TREM2) axis has been implicated in a large proportion of later-onset SAD (Shi and Holtzman, 2018). Specifically, the APOE genotype has been connected to amyloidogenic cleavage of APP within lipid rafts (Fuentealba et al., 2007).

TREM2 has been shown to promote the anti-inflammatory M2 microglial state characterized by increased production of Th2-biased cytokine interleukin 10 (IL-10) (Jevtic et al., 2017). Nonetheless, there are conflicting results as to whether relatively increased or decreased IL-10 levels are therapeutic in AD (Jevtic et al., 2017) and likely converge upon the fact that a delicate balance between pro- and anti-inflammatory CNS states exist, mediated by numerous cytokines, whose disruption is implicated in disease pathogenesis. Indeed, the current literature questions the validity of purely binary (M1/M2) microglial inflammatory states (Dionisio-Santos et al., 2019).

Recently, immunomodulation via purposely designed pharmacologic has surfaced as a potential avenue in AD treatment, where benzofuran derivatives have been noted for their antiamyloidogenic, neuroprotective properties, mediated purportedly via cannabinoid receptor antagonism and butyrylcholinesterase inhibition (Montanari et al., 2019). Also, resveratrol has been identified as a modulator of neuroinflammation, promoting inter alia increased levels of the anti-inflammatory IL-4, decreased CSF matrix metalloproteinase 9, and inducing adaptive immunity (Moussa et al., 2017). Interestingly, resveratrol strongly activates sirtuin 1 (SIRT1), an NAD+ dependent deacetylase that, deacetylating  $\tau$ , was shown to reduce tauopathy in a mouse model of the disease (Min et al., 2018). SIRT1 also promotes a physiological state resembling caloric restriction (Moussa et al., 2017). As caloric restriction induces sphingomyelin synthesis and sphingolipids are the building blocks for plasma membrane lipid rafts (Collet et al., 2017) which foster amyloidogenic cleavage of APP, further research on the intersection between SIRT1, ApoE, and amyloid fibril formation will be required to elucidate the therapeutic potential of resveratrol in AD treatment.

### 6. Conclusions

The involvement of the immune system in the pathogenesis of AD seems indisputable. However, many of the pathways linking immune responses to the development of neurodegeneration remain uncharacterized. Neither exactly how and when immune activation occurs in the course of AD, nor the extent of its impact on cognitive functions are known. How are microglia involved in the development of AD, and to what extent does physiological aging result in their impaired capacity for nervous tissue maintenance? Are reduced immune responses due to age or disease key factors in the pathogenesis of AD? How does the age-dependent reduction of T and B cell levels affect AD onset and progression? How effective are immunotherapies currently used to treat AD? While satisfactory answers to the above questions are presently unavailable, it seems indisputable that vaccines, together with pharmacologic modulation of immune responses may lead to prophylactic or therapeutic strategies in AD treatment in the future. Moreover, understanding the relationships between APOE, BIN1, and CLU described above may help to determine the risk of individuals with a positive family history of AD face of developing cognitive impairment. Nonetheless, preventive measures such as intellectual exercise, socialization, and proper diet, if undertaken by subjects at high risk of developing dementia, and especially those bearing unfavorable genetic variants of APOE, BIN1, and CLU, could contribute to delaying the onset of cognitive deterioration.

### Author contributions

MP, MK, ULJ, TP, AK, WK, and JD wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

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### **Conflict of Interest**

The authors declare no competing interests.

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#### References

- Aikawa, T., Holm, M. L. and Kanekiyo, T. (2018) ABCA7 and pathogenic pathways of Alzheimer's Disease. *Brain Sciences* 8, E27.
- Aikawa, T., Ren, Y., Yamazaki, Y., Tachibana, M., Johnson, M. R., Anderson, C. T., Martens, Y. A., Holm, M-L., Asmann, Y. W., Saito, T., Saido, T. C., Fitzgerald, M. L., Bu, G. and Kanekiyo, T. (2019) ABCA7 Haplodeficiency disturbs microglial immune responses in the mouse brain. *Proceeding of the National Academy of Sciences of the United States of America* **116**, 23790-23796.
- Almeida, J. F. F., Dos Santos, L. R., Trancozo, M. and de Paula, F. (2018) Updated meta-analysis of BIN1, CR1, MS4A6A, CLU, and ABCA7 variants in Alzheimer's Disease. *Journal of Molecular Neuroscience* 64, 471-477.
- Apostolova, L. G., Risacher, S. L., Duran, T., Stage, E. C., Goukasian, N., West, J. D., Do, T. M., Grotts, J., Wilhalme, H., Nho, K., Phillips, M., Elashoff, D. and Saykin, A. J. (2018) Associations of the top 20 Alzheimer's Disease risk variants with brain amyloidosis. *JAMA Neu*rology **75**, 328-341.
- Arold, S., Sullivan, P., Bilousova, T., Teng, E., Miller, C. A., Poon, W. W., Vinters, H. V., Cornwell, L. B., Saing, T., Cole, G. M. and Gylys, K. H. (2012) Apolipoprotein E level and cholesterol are associated with reduced synaptic amyloid beta in Alzheimer's Disease and apoE TR mouse cortex. *Acta Neuropathologica* 123, 39-52.
- Arriagada, P., Growdon, J., Hedley-Whyte, E. and Hyman, B. (1992) Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's Disease. *Neurology* 42, 631-631.
- Barba, R., Martínez-Espinosa, S., Rodríguez-García, E., Pondal, M., Vivancos, J. and Del Ser, T. (2000) Poststroke dementia: clinical features and risk factors. *Stroke* **31**, 1494-501.
- Barbier, P., Zejneli, O., Martinho, M., Lasorsa, A., Belle, V., Smet-Nocca, C., Tsvetkov, P., Devred, F. and Landrieu, I. (2019) Role of Tau as a microtubule-associated protein: Structural and functional aspects. *Frontiers in Aging Neuroscience* 11, 204.
- Bi, M., Ittner, A., Ke, Y., Götz, J. and Ittner, L. (2011) Tau-targeted immunization impedes progression of neurofibrillary histopathology in aged P301L Tau transgenic mice. *Plos One* 6, e26860.
- Blennow, K., de Leon, M. J. and Zetterberg, H. (2006) Alzheimer's Disease. *Lancet* 368, 387-403.
- Boimel, M., Grigoriadis, N., Lourbopoulos, A., Haber, E., Abramsky, O. and Rosenmann, H. (2010) Efficacy and safety of immunization with phosphorylated tau against neurofibrillary tangles in mice. *Experimental Neurology* 224, 472-485.
- Bressler, J., Mosley, T. H., Penman, A., Gottesman, R. F., Windham, B. G., Knopman, D. S., Wruck, L. M. and Boerwinkle, E. (2017) Genetic variants associated with risk of Alzheimer's Disease contribute to cognitive change in midlife: the atherosclerosis risk in communities study. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* 174, 269-282.
- Busse, M., Michler, E., von Hoff, F., Dobrowolny, H., Hartig, R., Frodl, T. and Busse, S. (2017) Alterations in the peripheral immune system in dementia. *Journal of Alzheimer's Disease* 58, 1303-1313.
- Cai, Z., Hussain, M. D. and Yan, L. J. (2014) Microglia, neuroinflammation, and beta-amyloid protein in Alzheimer's Disease. *International Journal of Neuroscience* 124, 307-321.
- Cao, W. and Zheng, H. (2018) Peripheral immune system in aging and Alzheimer's Disease. *Molecular Neurodegeneration* 13, 51.
- Carrano, A., Hoozemans, J. J., van der Vies, S. M., van Horssen, J., de Vries, H. E. and Rozemuller, A. J. (2012) Neuroinflammation and blood-brain barrier changes in capillary amyloid angiopathy. *Neurode-generative Diseases* 10, 329-331.
- Chan, G., White, C. C., Winn, P. A., Cimpean, M., Replogle, J. M., Glick, L. R., Cuerdon, N. E., Ryan, K. J., Johnson, K. A., Schneider, J. A.,

Bennett, D. A., Chibnik, L. B., Sperling, R. A., Bradshaw, E. M. and De Jager, P. L. (2015) CD33 modulates TREM2: convergence of Alzheimer loci. *Nature Neuroscience* **18**, 1556-1558.

- Chang, M. Y., Boulden, J., Katz, J. B., Wang, L., Meyer, T. J., Peralta Soler, A., Muller, A. J. and Prendergast, G. C. (2007) Bin1 ablation increases susceptibility to cancer during aging, particularly lung cancer. *Cancer Research* 67, 7605-7612.
- Chapuis, J., Hansmannel, F., Gistelinck, M., Mounier, A., Van Cauwenberghe, C., Kolen, K. V., Geller, F., Sottejeau, Y., Harold, D., Dourlen, P., Grenier-Boley, B., Kamatani, Y., Delepine, B., Demiautte, F., Zelenika, D., Zommer, N., Hamdane, M., Bellenguez, C., Dartigues, J. F., Hauw, J. J., Letronne, F., Ayral, A. M., Sleegers, K., Schellens, A., Broeck, L. V., Engelborghs, S., De Deyn, P. P., Vandenberghe, R., O'Donovan, M., Owen, M., Epelbaum, J., Mercken, M., Karran, E., Bantscheff, M., Drewes, G., Joberty, G., Campion, D., Octave, J. N., Berr, C., Lathrop, M., Callaerts, P., Mann, D., Williams, J., Buée, L., Dewachter, I., Van Broeckhoven, C., Amouyel, P., Moechars, D., Dermaut, B., Lambert, J. C. and GERAD consortium. (2013) Increased expression of BIN1 mediates Alzheimer genetic risk by modulating tau pathology. *Molecular Psychiatry* 18, 1225-1234.
- Chen, H., Wu, G., Jiang, Y., Feng, R., Liao, M., Zhang, L., Ma, G., Chen, Z., Zhao, B., Li, K., Yu, C. and Liu, G. (2015) Analyzing 54,936 samples supports the association between CD2AP rs9349407 polymorphism and Alzheimer's Disease susceptibility. *Molecular Neurobiology* 52, 1-7.
- Chouraki, V. and Seshadri, S. (2014) Genetics of Alzheimer's Disease. Advances in Genetics 87, 245-294.
- Cochran, J. N., Rush, T., Buckingham, S. C. and Roberson, E. D. (2015) The Alzheimer's Disease risk factor CD2AP maintains blood-brain barrier integrity. *Human Molecular Genetics* 24, 6667-6674.
- Collet, T., Sonoyama, T., Henning, E., Keogh, J., Ingram, B., Kelway, S., Guo, L. and Farooqi, I. (2017) A metabolomic signature of acute caloric restriction. *Journal of Clinical Endocrinology and Metabolism* **102**, 4486-4495.
- Corder, E. H. and Caskey, J. (2009) Early intervention in Alzheimer's Disease: the importance of APOE4 plus family history. *Neurology* 73, 2054-2055.
- Crotti, A., Sait, H. R., McAvoy, K. M., Estrada, K., Ergun, A., Szak, S., Marsh, G., Jandreski, L., Peterson, M., Reynolds, T. L., Dalkilic-Liddle, I., Cameron, A., Cahir-McFarland, E. and Ransohoff, R. M. (2019) BIN1 favors the spreading of Tau via extracellular vesicles. *Scientific Reports* 9, 9477.
- Cruchaga, C., Kauwe, J. S., Harari, O., Jin, S. C., Cai, Y., Karch, C. M., Benitez, B. A., Jeng, A. T., Skorupa, T., Carrell, D., Bertelsen, S., Bailey, M., McKean, D., Shulman, J. M., De Jager, P. L., Chibnik, L., Bennett, D. A., Arnold, S. E., Harold, D., Sims, R., Gerrish, A., Williams, J., Van Deerlin, V. M., Lee, V. M., Shaw, L. M., Trojanowski, J. Q., Haines, J. L., Mayeux, R., Pericak-Vance, M. A., Farrer, L. A., Schellenberg, G. D., Peskind, E. R., Galasko, D., Fagan, A. M., Holtzman, D. M., Morris, J. C., GERAD Consortium, Alzheimer's Disease Neuroimaging Initiative (ADNI), Alzheimer Disease Genetic Consortium (ADGC) and Goate, A. M. (2013) GWAS of cerebrospinal fluid tau levels identifies risk variants for Alzheimer's Disease. *Neuron* 78, 256-268.
- Cummins, T. D., Wu, K. Z. L., Bozatzi, P., Dingwell, K. S., Macartney, T. J., Wood, N. T., Varghese, J., Gourlay, R., Campbell, D. G., Prescott, A., Griffis, E., Smith, J. C. and Sapkota, G. P. (2018) PAWS1 controls cytoskeletal dynamics and cell migration through association with the SH3 adaptor CD2AP. *Journal of Cell Science* 131, jcs202390.
- Czirr, E., Castello, N. A., Mosher, K. I., Castellano, J. M., Hinkson, I. V., Lucin, K. M., Baeza-Raja, B., Ryu, J. K., Li, L., Farina, S. N., Belichenko, N. P., Longo, F. M., Akassoglou, K., Britschgi, M., Cirrito, J. R. and Wyss-Coray, T. (2017) Microglial complement receptor 3 regulates brain Aβ levels through secreted proteolytic activity. *Journal of Experimental Medicine* **214**, 1081-1092.
- Daborg, J., Andreasson, U., Pekna, M., Lautner, R., Hanse, E., Minthon, L., Blennow, K., Hansson, O. and Zetterberg, H. (2012) Cerebrospinal fluid levels of complement proteins C3, C4 and CR1 in Alzheimer's Disease. *Journal of Neural Transmission (Vienna)* 119, 789-797.

- Davalos, D., Grutzendler, J., Yang, G., Kim, J. V., Zuo, Y., Jung, S., Littman, D. R., Dustin, M. L. and Gan, W. B. (2005) ATP mediates rapid microglial response to local brain injury *in vivo*. *Nature Neuro-science* 8, 752-758.
- Deora, V., Lee, J., Albornoz, E., McAlary, L., Jagaraj, C., Robertson, A., Atkin, J., Cooper, M., Schroder, K., Yerbury, J., Gordon, R. and Woodruff, T. M. (2020) The microglial NLRP3 inflammasome is activated by amyotrophic lateral sclerosis proteins. *Glia* 68, 407-421.
- De Rossi, P., Buggia-Prevot, V., Andrew, R. J., Krause, S. V., Woo, E., Nelson, P. T., Pytel, P. and Thinakaran, G. (2017) BIN1 localization is distinct from Tau tangles in Alzheimer's Disease. *Matters (Zur)* 2017, 1-7.
- De Rossi, P., Nomura, T., Andrew, R. J., Masse, N. Y., Sampathkumar, V., Musial, T. F., Sudwarts, A., Recupero, A. J., Le Metayer, T., Hansen, M. T., Shim, H. N., Krause, S. V., Freedman, D. J., Bindokas, V. P., Kasthuri, N., Nicholson, D. A., Contractor, A. and Thinakaran, G. (2020) Neuronal BIN1 regulates presynaptic neurotransmitter release and memory consolidation. *Cell Reports* **30**, 3520-3535.
- Dionisio-Santos, D., Olschowka, J. and O'Banion, M. (2019) Exploiting microglial and peripheral immune cell crosstalk to treat Alzheimer's Disease. *Journal of Neuroinflammation* 16, 74.
- Dong, X., Zhang, L., Meng, Q. and Gao, Q. (2017) Association between Interleukin-1A, Interleukin-1B, and bridging integrator 1 polymorphisms and Alzheimer's Disease: a standard and cumulative metaanalysis. *Molecular Neurobiology* 54, 736-747.
- Dorszewska, J., Prendecki, M., Oczkowska, A., Dezor, M. and Kozubski, W. (2016) Molecular basis of familial and sporadic Alzheimer's Disease. *Current Alzheimer Research* 13, 952-963.
- Dorszewska, J., Prendecki, M., Florczak-Wyspiańska, J., Ilkowski, J. and Kozubski, W. (2019) Genetic variants of CLU (rs9331896) and BIN1 (rs6733839) in Alzheimer's Disease: patients carriers and non-carriers of APOE4 allele. *Alzheimer's and Dementia* 15, P1354-P1355.
- Du, W., Tan, J., Xu, W., Chen, J. and Wang, L. (2016) Association between clusterin gene polymorphism rs11136000 and late-onset Alzheimer's Disease susceptibility: a review and meta-analysis of case-control studies. *Experimental and Therapeutic Medicine* 12, 2915-2927.
- Dustin, M. L., Olszowy, M. W., Holdorf, A. D., Li, J., Bromley, S., Desai, N., Widder, P., Rosenberger, F., van der Merwe, P. A., Allen, P. M. and Shaw, A. S. (1998) A novel adaptor protein orchestrates receptor patterning and cytoskeletal polarity in T-cell contacts. *Cell* 94, 667-677.
- Edison, P., Archer, H. A., Gerhard, A., Pavese, N., Turkheimer, F. E., Hammers, A., Fong Tai, Y., Fox, N., Kennedy, A., Rossor, M. and Brooks D. J. (2008) Microglia, amyloid, and cognition in Alzheimer's Disease: an [11C] (R)PK11195-PET and [11C] PIB-PET study. *Neurobiology of Disease* 32, 412-419.
- Filipello, F., Morini, R., Corradini, I., Zerbi, V., Canzi, A., Michalski, B., Erreni, M., Markicevic, M., Starvaggi-Cucuzza, C., Otero, K., Piccio, L., Cignarella, F., Perrucci, F., Tamborini, M., Genua, M., Rajendran, L., Menna, E., Vetrano, S., Fahnestock, M., Paolicelli, R. C. and Matteoli, M. (2018) The microglial innate immune receptor TREM2 is required for synapse elimination and normal brain connectivity. *Immunity* 48, 979-991.
- Fonseca, M, I., Chu, S., Pierce, A. L., Brubaker, W. D., Hauhart, R. E., Mastroeni, D., Clarke, E. V., Rogers, J., Atkinson, J. P. and Tenner, A. J. (2016) Analysis of the putative role of CR1 in Alzheimer's Disease: genetic association, expression and function. *PLoS One* 11, e0149792.
- Foster, E. M., Dangla-Valls, A., Lovestone, S., Ribe, E. M. and Buckley, N. J. (2019) Clusterin in Alzheimer's Disease: mechanisms, genetics, and lessons from other pathologies. *Frontiers in Neuroscience* 13, 164.
- Frost, G. R., Jonas, L. A and Li, Y. M. (2019) Friend, Foe or both? Immune activity in Alzheimer's Disease. *Frontiers in Aging Neuroscience* 11, 337.
- Fuentealba, R., Barría, M., Lee, J., Cam, J., Araya, C., Escudero, C., Inestrosa, N., Bronfman, F., Bu, G. and Marzolo, M. (2007) ApoER2 expression increases  $A\beta$  production while decreasing Amyloid Precursor Protein (APP) endocytosis: possible role in the partitioning of APP into lipid rafts and in the regulation of  $\gamma$ -secretase activity. *Molecular Neurodegeneration* **2**, 14.

- Gate, D., Saligrama, N., Leventhal, O., Yang, A. C., Unger, M. S., Middeldorp, J., Chen, K., Lehallier, B., Channappa, D., De Los Santos, M. B., McBride, A., Pluvinage, J., Elahi, F., Tam, G. K., Kim, Y., Greicius, M., Wagner, A. D., Aigner, L., Galasko, D. R., Davis, M. M. and Wyss-Coray, T. (2020) Clonally expanded CD8 T cells patrol the cerebrospinal fluid in Alzheimer's Disease. *Nature* 577, 399-404.
- Ginhoux, F., Greter, M., Leboeuf, M., Nandi, S., See, P., Gokhan, S., Mehler, M. F., Conway, S. J., Guan Ng, L., Stanley, E. R., Samokhvalov, I. M. and Merad, M. (2010) Fate mapping analysis reveals that adult microglia derive from primitive macrophages. *Science* 330, 841-845.
- Giri, M., Zhang, M. and Lü, Y. (2016) Genes associated with Alzheimer's Disease: an overview and current status. *Clinical Interventions in Aging* **11**, 665-681.
- Greenbaum, L., Ravona-Springer, R., Lubitz, I., Schmeidler, J., Cooper, I., Sano, M., Silverman, J. M., Heymann, A. and Beeri, M. S. (2016) Potential contribution of the Alzheimer's Disease risk locus BIN1 to episodic memory performance in cognitively normal Type 2 diabetes elderly. *European Neuropsychopharmacology* 26, 787-795.
- Griciuc, A., Serrano-Pozo, A., Parrado, A. R., Lesinski, A. N., Asselin, C. N., Mullin, K., Hooli, B., Choi, S. H., Hyman, B. T. and Tanzi, R. E. (2013) Alzheimer's Disease risk gene CD33 inhibits microglial uptake of amyloid beta. *Neuron* 78, 631-643.
- Griciuc, A., Patel, S., Federico, A. N., Choi, S. H., Innes, B. J., Oram, M. K., Cereghetti, G., McGinty, D., Anselmo, A., Sadreyev, R. I., Hickman, S. E., El Khoury, J., Colonna, M. and Tanzi, R. (2019) TREM2 acts downstream of CD33 in modulating microglial pathology in Alzheimer's Disease. *Neuron* 103, 820-835.
- Griffin, W. S., Stanley, L. C., Ling, C., White, L., MacLeod, V., Perrot, L. J., White, C. L., 3<sup>rd</sup>. and Araoz, C. (1989) Brain interleukin 1 and S-100 immunoreactivity are elevated in Down syndrome and Alzheimer's Disease. *Proceedings of the National Academy of Sciences of the United States of America* 86, 7611-7615.
- Guerriero, F., Sgarlata, C., Francis, M., Maurizi, N., Faragli, A., Perna, S., Rondanelli, M., Rollone, M. and Ricevuti, G. (2017) Neuroinflammation, immune system and Alzheimer Disease: searching for the missing link. *Aging Clinical and Experimental Research* 29, 821-831.
- Halle, A., Hornung, V., Petzold, G. C., Stewart, C. R., Monks, B. G., Reinheckel, T., Fitzgerald, K. A., Latz, E., Moore, K. J. and Golenbock, D. T. (2008) The NALP3 inflammasome is involved in the innate immune response to amyloid-beta. *Nature Immunology* 9, 857-865.
- Han, Z., Qu, J., Zhao, J. and Zou, X. (2018) Analyzing 74,248 samples confirms the association between CLU rs11136000 polymorphism and Alzheimer's Disease in caucasian but not Chinese population. *Scientific Reports* 8, 11062.
- Han, Z., Wang, T., Tian, R., Zhou, W., Wang, P., Ren, P., Zong, J., Hu, Y., Jin, S. and Jiang, Q. (2019) BIN1 rs744373 variant shows different association with Alzheimer's Disease in Caucasian and Asian populations. *BMC Bioinformatics* 20, 691.
- Hansen, D. V., Hanson, J. E. and Sheng, M. (2018) Microglia in Alzheimer's Disease. *Journal of Cell Biology* 217, 459-472.
- Heneka, M. T., Carson, M. J., El Khoury, J., Landreth, G. E., Brosseron, F., Feinstein, D. L., Jacobs, A. H., Wyss-Coray, T., Vitorica, J., Ransohoff, R. M., Herrup, K., Frautschy, S. A., Finsen, B., Brown, G. C., Verkhratsky, A., Yamanaka, K., Koistinaho, J., Latz, E., Halle, A., Petzold, G. C., Town, T., Morgan, D., Shinohara, M. L., Perry, V. H., Holmes, C., Bazan, N. G., Brooks, D. J., Hunot, S., Joseph, B., Deigendesch, N., Garaschuk, O., Boddeke, E., Dinarello, C. A., Breitner, J. C., Cole, G. M., Golenbock, D. T. and Kummer, M. P. (2015) Neuroinflammation in Alzheimer's Disease. *Lancet Neurology* 14, 388-405.
- Heppner, F. L., Ransohoff, R. M. and Becher, B. (2015) Immune attack: the role of inflammation in Alzheimer's Disease. *Nature Reviews Neuroscience* 16, 358-372.
- Hickman, S., Izzy, S., Sen, P., Morsett, L. and El Khoury, J. (2018) Microglia in neurodegeneration. *Nature Neuroscience* 21, 1359-1369.
- Hill, E., Karikari, T., Moffat, K., Richardson, M. and Wall, M. (2019) Introduction of Tau oligomers into cortical neurons alters action potential dynamics and disrupts synaptic transmission and plasticity. *eNeuro* 6, 1-20.

- Holers, V. M. (2014) Complement and its receptors: new insights into human disease. *Annual Review of Immunology* **32**, 433-459.
- Hollingworth, P., Harold, D., Sims, R., Gerrish, A., Lambert, J. C., Carrasquillo, M. M., Abraham, R., Hamshere, M. L., Pahwa, J. S., Moskvina, V. and Study Group. (2011) Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's Disease. *Nature Genetics* 43, 429-435.
- Hong, S., Beja-Glasser, V. F., Nfonoyim, B. M., Frouin, A., Li, S., Ramakrishnan, S., Merry, K. M., Shi, Q., Rosenthal, A., Barres, B. A., Lemere, C. A., Selkoe, D. J. and Stevens, B. (2016) Complement and microglia mediate early synapse loss in Alzheimer mouse models. *Science* 352, 712-716.
- Huang, T. Y. and Xu, H. (2019) Bringing order out of chaos: establishing an epistatic relationship between CD33 and TREM2. *Neuron* 103, 747-749.
- Ide, M., Harris, M., Stevens, A., Sussams, R., Hopkins, V., Culliford, D., Fuller, J., Ibbett, P., Raybould, R., Thomas, R., Puenter, U., Teeling, J., Perry, V. H. and Holmes, C. (2016) Periodontitis and cognitive decline in Alzheimer's Disease. *PLoS One* **11**, e0151081.
- Ieguchi, K. and Maru, Y. (2019) Roles of EphA1/A2 and ephrin-A1 in cancer. *Cancer Science* **110**, 841-848.
- Ismail, R., Parbo, P., Stensvig Madsen, L., Hansen, A. K., Hansen, K. V., Schaldemose, J. L., Kjeldsen, P. L., Stokholm, M. G., Gottrup, H., Eskildsen, S. F. and Brooks, D. J. (2020) The relationships between neuroinflammation, beta-amyloid and Tau deposition in Alzheimer's Disease: a longitudinal PET study. *Journal of Neuroinflammation* 17, 151.
- Iwamoto, N., Abe-Dohmae, S., Sato, R. and Yokoyama, S. (2006) ABCA7 expression is regulated by cellular cholesterol through the SREBP2 pathway and associated with phagocytosis. *Journal of Lipid Research* 47, 1915-1927.
- Jack, C. R. Jr., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., Holtzman, D. M., Jagust, W., Jessen, F., Karlawish, J., Liu, E., Molinuevo, J. L., Montine, T., Phelps, C., Rankin, K. P., Rowe, C. C, Scheltens, P., Siemers, E., Snyder, H. M. and Sperling, R. (2018) NIA-AA research framework: toward a biological definition of Alzheimer's Disease. *Alzheimer's and Dementia* 14, 535-562.
- Jansen, I. E., Savage, J. E., Watanabe, K., Bryois, J., Williams, D. M., Steinberg, S., Sealock, J., Karlsson, I. K., Hägg, S., Athanasiu, L., Voyle, N., Proitsi, P., Witoelar, A., Stringer, S., Aarsland, D., Almdahl. I. S., Andersen, F., Bergh, S., Bettella, F., Bjornsson, S., Brækhus, A., Bråthen, G., de Leeuw, C., Desikan, R. S., Djurovic, S., Dumitrescu, L., Fladby, T., Hohman, T. J., Jonsson, P. V., Kiddle, S. J., Rongve, A., Saltvedt, I., Sando, S. B., Selbæk, G., Shoai, M., Skene, N. G., Snaedal, J., Stordal, E., Ulstein, I. D., Wang, Y., White, L. R., Hardy, J., Hjerling-Leffler, J., Sullivan, P. F., van der Flier, W. M., Dobson, R., Davis, L. K., Stefansson, H., Stefansson, K., Pedersen, N. L., Ripke, S., Andreassen, O. A. and Posthuma, D. (2019) Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's Disease risk. *Nature Genetics* **51**, 404-413.
- Jevtic, S., Sengar, A., Salter, M. and McLaurin, J. (2017) The role of the immune system in Alzheimer's Disease: etiology and treatment. Ageing Research Reviews 40, 84-94.
- Jiang, T., Hou, J. K., Gao, Q., Yu, J. T., Zhou, J. S., Zhao, H. D. and Zhang, Y. D. (2016) TREM2 p.H157Y variant and the risk of Alzheimer's Disease: a meta-analysis involving 14,510 subjects. *Current Neurovascular Research* 13, 318-320.
- Jorda, A., Campos-Campos, J., Iradi, A., Aldasoro, M., Aldasoro, C., Vila, J. M. and Valles, S. L. (2020) 'The role of chemokines in Alzheimer's Disease'. *Endocrine, Metabolic and Immune Disorders Drug Targets* (in press).
- Juul Rasmussen, I., Tybjærg-Hansen, A., Rasmussen, K. L., Nordestgaard, B. G. and Frikke-Schmidt, R. (2019) Blood-brain barrier transcytosis genes, risk of dementia and stroke: a prospective cohort study of 74,754 individuals. *European Journal of Epidemiology* 34, 579-590.
- Karch, C. M., Jeng, A. T., Nowotny, P., Cady, J., Cruchaga, C. and Goate, A. M. (2012) Expression of novel Alzheimer's Disease risk genes in control and Alzheimer's Disease brains. *PLoS One* 7, e50976.

Karch, C. M. and Goate, A. M. (2015) Alzheimer's Disease risk genes and mechanisms of disease pathogenesis. *Biological Psychiatry* 77, 43-51.

- Katsel, P. and Haroutunian, V. (2019) Is Alzheimer Disease a failure of mobilizing immune defense? Lessons from cognitively fit oldest-old. *Dialogues in Clinical Neuroscience* 21, 7-19.
- Kfoury, N., Holmes, B., Jiang, H., Holtzman, D. and Diamond, M. (2012) Trans-cellular propagation of Tau aggregation by fibrillar species. *Journal of Biological Chemistry* 287, 19440-19451.
- Khan, H., Rafiq, A., Shabaneh, O., Gittner, L. S. and Reddy, P. H. (2019) Current issues in chronic diseases: a focus on dementia and hypertension in rural west Texans. *Journal of Alzheimer's Disease* 72, S59-S69.
- Kim, W. S., Guillemin, G. J., Glaros, E. N., Lim, C. K. and Garner, B. (2006) Quantitation of ATP-binding cassette subfamily-a transporter gene expression in primary human brain cells. *Neuroreport* 17, 891-896.
- Kim, W. S., Li, H., Ruberu, K., Chan, S., Elliott, D. A., Low, J. K., Cheng, D., Karl, T. and Garner, B. (2013) Deletion of Abca7 increases cerebral amyloid-β accumulation in the J20 mouse model of Alzheimer's Disease. *Journal of Neuroscience* 33, 4387-4394.
- Kirszbaum, L., Bozas, S. E. and Walker, I. D. (1992) SP-40,40, a protein involved in the control of the complement pathway, possesses a unique array of disulphide bridges. *FEBS Letters* 297, 70-76.
- Kolaczkowska, E. and Kubes, P. (2013) Neutrophil recruitment and function in health and inflammation. *Nature Reviews Immunology* 13, 159-175.
- Kowalska, M., Wize, K., Prendecki, M., Lianeri, M., Kozubski, W. and Dorszewska, J. (2020) 'Genetic variants and oxidative stress in Alzheimer's Disease'. *Current Alzheimer Research (in press)*.
- Krasemann, S., Madore, C., Cialic, R., Baufeld, C., Calcagno, N., El Fatimy, R., Beckers, L., O'Loughlin, E., Xu, Y., Fanek, Z., Greco, D. J., Smith, S. T., Tweet, G., Humulock, Z., Zrzavy, T., Conde-Sanroman, P., Gacias, M., Weng, Z., Chen, H., Emily Tjon, E., Mazaheri, F., Hartmann, K., Madi, A., Ulrich, J. D., Glatzel, M., Worthmann, A., Heeren, J., Budnik, B., Lemere, C., Ikezu, T., Heppner, F. L., Litvak, V., Holtzman, D. M., Lassmann, H., Weiner, H. L., Ochando, J., Haass, C. and Butovsky, O. (2017) The TREM2-APOE pathway drives the transcriptional phenotype of dysfunctional microglia in neurodegenerative diseases. *Immunity* 47, 566-581.
- Kunkle, B. W., Grenier-Boley, B., Sims, R., Bis, J. C., Damotte, V., Naj, A. C., Boland, A., Vronskaya, M., van der Lee, S. J., Amlie-Wolf, A. and Study Group. (2019) Author correction: genetic meta-analysis of diagnosed Alzheimer's Disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing. *Nature Genetics* **51**, 414-430.
- Lambert, J. C., Ibrahim-Verbaas, C. A., Harold, D., Naj, A. C., Sims, R., Bellenguez, C., DeStafano, A. L., Bis, J. C., Beecham, G. W., Grenier-Boley, B., Russo, G., Thorton-Wells, T. A. and IGAP Study Group (2013) Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's Disease. *Nature Genetics* 45, 1452-1458.
- Lee, C. Y. D., Daggett, A., Gu, X., Jiang, L. L., Langfelder, P., Li, X., Wang, N., Zhao, Y., Park, C. S., Cooper, Y., Ferando, I., Mody, I., Coppola, G., Xu, H. and Yang, X. W. (2018) Elevated TREM2 gene dosage reprograms microglia responsivity and ameliorates pathological phenotypes in Alzheimer's Disease models. *Neuron* 97, 1032-1048.
- Li, J. Q., Wang, H. F., Zhu, X. C., Sun, F. R., Tan, M. S., Tan, C. C., Jiang, T., Tan, L. and Yu, J. T. and Alzheimer's Disease Neuroimaging Initiative. (2017) GWAS-linked loci and neuroimaging measures in Alzheimer's Disease. *Molecular Neurobiology* 54, 146-153.
- Lian, H., Yang, L., Cole, A., Sun, L., Chiang, A. C., Fowler, S. W., Shim, D. J., Rodriguez-Rivera, J., Taglialatela, G., Jankowsky, J. L., Lu, H. C. and Zheng, H. (2015) NFκB-activated astroglial release of complement C3 compromises neuronal morphology and function associated with Alzheimer's Disease. *Neuron* 85, 101-115.
- Liu, D., Cao, B., Zhao, Y., Huang, H., McIntyre, R. S., Rosenblat, J. D. and Zhou, H. (2018) Soluble TREM2 changes during the clinical course of Alzheimer's Disease: a meta-analysis. *Neuroscience Letters* 686, 10-16.
- Lu, Y., Liu, W. and Wang, X. (2015) TREM2 variants and risk of Alzheimer's Disease: a meta-analysis. *Neurological Sciences* 36, 1881-1888.

- Ma, Q., Zhao, Z., Sagare, A. P., Wu, Y., Wang, M., Chuqui Owens, N., Verghese, P. B., Herz, J., Holtzman, D. M. and Zlokovic, B. (2018) Blood-brain barrier-associated pericytes internalize and clear aggregated amyloid-β42 by LRP1-dependent apolipoprotein E isoformspecific mechanism. *Molecular Neurodegeneration* 13, 57.
- Maier, M., Peng, Y., Jiang, L., Seabrook, T. J., Carroll, M. C. and Lemere, C. A. (2008) Complement C3 deficiency leads to accelerated amyloid beta plaque deposition and neurodegeneration and modulation of the microglia/macrophage phenotype in amyloid precursor protein transgenic mice. *Journal of Neuroscience* 28, 6333-6341.
- Marioni, R. E., Harris, S. E., Zhang, Q., McRae, A. F., Hagenaars, S. P., Hill, W. D., Davies, G., Ritchie, C. W., Gale, C. R., Starr, J. M., Goate, A. M., Porteous, D. J., Yang, J., Evans, K. L., Deary, I. J., Wray, N. R. and Visscher, P. M. (2018) GWAS on family history of Alzheimer's Disease. *Translational Psychiatry* 8, 99.
- Marsh, S. E., Abud, E. M., Lakatos, A., Karimzadeh, A., Yeung, S. T., Davtyan, H., Fote, G. M., Lau, L., Weinger, J. G., Lane, T. E., Inlay, M. A., Poon, W. W. and Blurton-Jones, M. (2016) The adaptive immune system restrains Alzheimer's Disease pathogenesis by modulating microglial function. *Proceedings of the National Academy of Sciences* 113, E1316-E1325.
- Martinez, A., Otal, R., Sieber, B. A., Ibanez, C. and Soriano, E. (2005) Disruption of ephrin-A/EphA binding alters synaptogenesis and neural connectivity in the hippocampus. *Neuroscience* 135, 451-461.
- Mayeux, R. and Stern, Y. (2012) Epidemiology of Alzheimer's Disease. Cold Spring Harbor Perspectives in Medicine 2, a006239.
- McAvoy, K. M., Rajamohamed Sait, K., Marsh, G., Peterson, M., Reynolds, T. L., Gagnon, J., Geisler, S., Leach, P., Roberts, C., Cahir-McFarland, E., Ransohoff, R. M. and Crotti A. (2019) Cellautonomous and non-cell autonomous effects of neuronal BIN1 loss in vivo. PLoS One 14, e0220125.
- McManus, R. M., Mills, K. H. and Lynch, M. A. (2015) T cells-protective or pathogenic in Alzheimer's Disease? *Journal of Neuroimmune Pharmacology* 10, 547-560.
- McMillan, C. T., Lee, E. B., Jefferson-George, K., Naj, A., Van Deerlin, V. M., Trojanowski, J. Q. and Wolk, D. A. (2018) Alzheimer's genetic risk is reduced in primary age-related tauopathy: a potential model of resistance? *Annals of Clinical and Translational Neurology* 5, 927-934.
- McQuade, A. and Blurton-Jones, M. (2019) Microglia in Alzheimer's Disease: Exploring how genetics and phenotype influence risk. *Journal of Molecular Biology* 431, 1805-1817.
- Meilandt, W. J., Ngu, H., Gogineni, A., Lalehzadeh, G., Lee, S.-H., Srinivasan, H., Imperio, J., Wu, T., Weber, M., Kruse, A. J., Stark, K. L., Chan, P., Kwong, M., Modrusan, Z., Friedman, B. A., Elstrott, J., Foreman, O., Easton, A., Sheng, M. and Hansen. D. V. (2020) Trem2 deletion reduces late-stage amyloid plaque accumulation, elevates the Aβ42 : Aβ40 ratio, and exacerbates axonal dystrophy and dendritic spine loss in the PS2APP Alzheimer's mouse model. *Journal of Neuroscience* **40**, 1956-1974.
- Mildner, A., Schmidt, H., Nitsche, M., Merkler, D., Hanisch, U. K., Mack, M., Heikenwalder, M., Brück, W., Priller, J. and Prinz, M. (2007) Microglia in the adult brain arise from Ly-6ChiCCR2+ monocytes only under defined host conditions. *Nature Neuroscience* 10, 1544-1553.
- Min, S., Sohn, P., Li, Y., Devidze, N., Johnson, J., Krogan, N., Masliah, E., Mok, S., Gestwicki, J. and Gan, L. (2018) SIRT1 deacetylates Tau and reduces pathogenic Tau spread in a mouse model of tauopathy. *Journal* of Neuroscience 38, 3680-3688.
- Miners, J. S., Clarke, P. and Love, S. (2017) Clusterin levels are increased in Alzheimer's Disease and influence the regional distribution of Aβ. *Brain Pathology* 27, 305-313.
- Miyagawa, T., Ebinuma, I., Morohashi, Y., Hori, Y., Young Chang, M., Hattori, H., Machara, T., Yokoshima, S., Fukuyama, T., Tsuji, S., Iwatsubo, T., Prendergast, G. C. and Tomita, T. (2016) BIN1 regulates BACE1 intracellular trafficking and amyloid-β production. *Human Molecular Genetics* 25, 2948-2958.
- Montanari, S., Mahmoud, A., Pruccoli, L., Rabbito, A., Naldi, M., Petralla, S., Moraleda, I., Bartolini, M., Monti, B., Iriepa, I, Belluti, F., Gobbi, S., Di Marzo, V., Bisi, A., Tarozzi, A., Ligresti, A. and Rampa, A. (2019) Discovery of novel benzofuran-based compounds with neuro-

protective and immunomodulatory properties for Alzheimer's Disease treatment. *European Journal of Medicinal Chemistry* **178**, 243-258.

- Moreno-Grau, S., de Rojas, I., Hernández, I., Quintela, I., Montrreal, L., Alegret, M., Hernández-Olasagarre, B., Madrid, L., González-Perez, A., Maroñas, O., Rosende-Roca, M., Mauleón, A., Vargas, L., Lafuente, A., Abdelnour, C., Rodríguez-Gómez, O., Gil, S., Santos-Santos, M. Á., Espinosa, A., Ortega, G., Sanabria, Á., Pérez-Cordón, A., Cañabate, P., Moreno, M., Preckler, S., Ruiz, S., Aguilera, N., Pineda, J. A., Macías, J., Alarcón-Martín, E., Sotolongo-Grau, O., GR@ACE consortium, DEGESCO consortium, Alzheimer's Disease Neuroimaging Initiative, Marquié, M., Monté-Rubio, G., Valero, S., Benaque, A., Clarimón, J., Bullido, M. J., García-Ribas, G., Pástor, P., Sánchez-Juan, P., Álvarez, V., Piñol-Ripoll, G., García-Alberca, J. M., Royo, J. L., Franco, E., Mir, P., Calero, M., Medina, M., Rábano, A., Ávila, J., Antúnez, C., Real, L. M., Orellana, A., Carracedo, Á., Sáez, M. E., Tárraga, L., Boada, M. and Ruiz, A. (2019) Genomewide association analysis of dementia and its clinical endophenotypes reveal novel loci associated with Alzheimer's Disease and three causality networks: The GR@ACE project. Alzheimer's and Dementia 15, 1333-1347
- Moussa, C., Hebron, M., Huang, X., Ahn, J., Rissman, R., Aisen, P. and Turner, R. (2017) Resveratrol regulates neuro-inflammation and induces adaptive immunity in Alzheimer's Disease. *Journal of Neuroinflammation* 14, 1.
- Naj, A. C., Jun, G., Beecham, G. W., Wang, L. S., Vardarajan, B. N., Buros, J., Gallins, P. J., Buxbaum, J. D., Jarvik, G. P., Crane, P. K. and Study Group. (2011) Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's Disease. *Nature Genetics* 43, 436-441.
- Nordestgaard, L. T., Tybjærg-Hansen, A., Rasmussen, K. L., Nordestgaard, B. G. and Frikke-Schmidt, R. (2018) Genetic variation in clusterin and risk of dementia and ischemic vascular disease in the general population: cohort studies and meta-analyses of 362,338 individuals. *BMC Medicine* 16, 39.
- Nuutinena, T., Suuronena, T., Kauppinena, A. and Salminenab, A. (2009) Clusterin: a forgotten player in Alzheimer's Disease. *Brain Research Reviews* 61, 89-104
- Ovsepian, S. V., O'Leary, V. B., Zaborszky, L., Ntziachristos, V. and Dolly, J. O. (2018) Synaptic vesicle cycle and amyloid  $\beta$ : Biting the hand that feeds. *Alzheimer's and Dementia* **14**, 502-513.
- Parhizkar, S., Arzberger, T., Brendel, M., Kleinberger, G., Deussing, M., Focke, C., Nuscher, B., Xiong, M., Ghasemigharagoz, A., Katzmarski, N., Krasemann, S., Lichtenthaler, S. F., Müller, S. A., Colombo, A., Sebastian Monasor, L., Tahirovic, S., Herms, J., Willem, M., Pettkus, N., Butovsky, O., Bartenstein, P., Edbauer, D., Rominger, A., Ertürk, A., Grathwohl, S. A., Neher, J. J., Holtzman, D. M., Meyer-Luehmann, M. and Haass, C. (2019) Loss of TREM2 function increases amyloid seeding but reduces plaque-associated ApoE. *Nature Neurosciences* 22, 191-204.
- Paul, S. P., Taylor, L. S., Stansbury, E. K. and McVicar, D. W. (2000) Myeloid specific human CD33 is an inhibitory receptor with differential ITIM function in recruiting the phosphatases SHP-1 and SHP-2. *Blood* 96, 483-490.
- Pendlebury, S. T., Poole, D., Burgess, A., Duerden, J. and Rothwell, P. M. and Oxford Vascular Study. (2020) APOE-ɛ4 genotype and dementia before and after transient ischemic attack and stroke: population-based cohort study. *Stroke* 51, 751-758.
- Polyak, M. J., Li, H., Shariat, N. and Deans, J. P. (2008) CD20 homooligomers physically associate with the B cell antigen receptor. Dissociation upon receptor engagement and recruitment of phosphoproteins and calmodulin-binding proteins. *Journal of Biological Chemistry* 283, 18545-18552.
- Prendecki, M., Florczak-Wyspianska, J., Kowalska, M., Lianeri, M., Kozubski, W. and Dorszewska, J. (2016) Update on dementia (2016) In, Moretti, D. V. (eds.) Normal aging and dementia (pp. 251-272). Rijeka, CA: InTech.
- Prendecki, M., Florczak-Wyspianska, J., Kowalska, M., Ilkowski, J., Grzelak, T., Bialas, K., Wiszniewska, M., Kozubski, W. and Dorszewska, J. (2018) Biothiols and oxidative stress markers and poly-

morphisms of TOMM40 and APOC1 genes in Alzheimer's Disease patients. *Oncotarget* 9, 35207-35225.

- Prendecki, M., Florczak-Wyspianska, J., Kowalska, M., Ilkowski, J., Grzelak, T., Bialas, K., Kozubski, W. and Dorszewska, J. (2019) APOE genetic variants and apoE, miR-107 and miR-650 levels in Alzheimer's Disease. *Folia Neuropathologica* 57, 106-116.
- Qi, X. M., Wang, C., Chu, X. K., Li, G. and Ma, J. F. (2018) Intraventricular infusion of clusterin ameliorated cognition and pathology in Tg6799 model of Alzheimer's Disease. *BMC Neuroscience* 19, 2.
- Rangaraju, S., Dammer, E. B., Raza, S. A., Gao, T., Xiao, H., Betarbet, R., Duong, D. M., Webster, J. A., Hales, C. M., Lah, J. J., Levey, A. I. and Seyfried, N. T. (2018) Quantitative proteomics of acutely-isolated mouse microglia identifies novel immune Alzheimer's Disease-related proteins. *Molecular Neurodegeneration* 13, 34.
- Ransohoff, R. M. (2016) How neuroinflammation contributes to neurodegeneration. *Science* 353, 777-783.
- Rasmussen, K. L., Tybjærg-Hansen, A., Nordestgaard, B. G. and Frikke-Schmidt, R. (2019) Plasma levels of apolipoprotein E, APOE genotype, and all-cause and cause-specific mortality in 105 949 individuals from a white general population cohort. *European Heart Journal* 40, 2813-2824.
- Rastas, S., Pirttilä, T., Mattila, K., Verkkoniemi, A., Juva, K., Niinistö, L., Länsimies, E. and Sulkava, R. (2010) Vascular risk factors and dementia in the general population aged > 85 years: prospective populationbased study. *Neurobiology of Aging* **31**, 1-7.
- Remarque, E. J., Bollen, E. L., Weverling-Rijnsburger, A. W., Laterveer, J. C., Blauw, G. J. and Westendorp, R. G. (2001) Patients with Alzheimer's Disease display a pro-inflammatory phenotype. *Experimental Gerontology* 36, 171-176.
- Rosenmann, H., Grigoriadis, N., Karussis, D., Boimel, M., Touloumi, O., Ovadia, H. and Abramsky, O. (2006) Tauopathy-like abnormalities and neurologic deficits in mice immunized with neuronal Tau protein. *Archives of Neurology* 63, 1459.
- Rozenstein-Tsalkovich, L., Grigoriadis, N., Lourbopoulos, A., Nousiopoulou, E., Kassis, I., Abramsky, O., Karussis, D. and Rosenmann, H. (2013) Repeated immunization of mice with phosphorylated-tau peptides causes neuroinflammation. *Experimental Neurology* 248, 451-456.
- Santos, L. R. D., Almeida, J. F. F., Pimassoni, L. H. S., Morelato, R. L. and Paula, F. (2020) The combined risk effect among BIN1, CLU, and APOE genes in Alzheimer's Disease. *Genetics and Molecular Biology* 43, e20180320.
- Saresella, M., Calabrese, E., Marventano, I., Piancone, F., Gatti, A., Calvo, M. G., Nemni, R. and Clerici, M. (2010) PD1 negative and PD1 positive CD4+ T regulatory cells in mild cognitive impairment and Alzheimer's Disease. *Journal of Alzheimer's Disease* 21, 927-938.
- Saunders, A. M. (2000) Apolipoprotein E and Alzheimer Disease: an update on genetic and functional analyses. *Journal of Neuropathology* and Experimental Neurology 59, 751-758.
- Schroeder, S., Joly-Amado, A., Gordon, M. and Morgan, D. (2015) Tau-directed immunotherapy: A promising strategy for treating Alzheimer's Disease and other Tauopathies. *Journal of Neuroimmune Pharmacology* 11, 9-25.
- Shen, Y., Lue, L., Yang, L., Roher, A., Kuo, Y., Strohmeyer, R., Goux, W. J., Lee, V., Johnson, G. V., Webster, S. D., Cooper, N. R., Bradt, B. and Rogers, J. (2001) Complement activation by neurofibrillary tangles in Alzheimer's Disease. *Neuroscience Letters* **305**, 165-168.
- Shi, Y. and Holtzman, D. (2018) Interplay between innate immunity and Alzheimer's Disease: APOE and TREM2 in the spotlight. *Nature Reviews Immunology* 18, 759-772.
- Shuai, P., Liu, Y., Lu, W., Liu, Q., Li, T. and Gong, B. (2015) Genetic associations of CLU rs9331888 polymorphism with Alzheimer's Disease: A meta-analysis. *Neuroscience Letters* 591, 160-165.
- Sigurdsson, E. (2008) Immunotherapy targeting pathological Tau protein in Alzheimer's Disease and related Tauopathies. *Journal of Alzheimer's Disease* 15, 157-168.
- Sigurdsson, E. (2009) Tau-focused immunotherapy for Alzheimer's Disease and related Tauopathies. *Current Alzheimer Research* 6, 446-450.

- Steinberg, S., Stefansson, H., Jonsson, T., Johannsdottir, H., Ingason, A., Helgason, H., Sulem, P., Magnusson, O. T., Gudjonsson, S. A., Unnsteinsdottir, U., Kong, A., Helisalmi, S., Soininen, H., Lah, J. J., Gene, D., Aarsland, D., Fladby, T., Ulstein, I. D., Djurovic, S., Sando, S. B., White, L. R., Knudsen, G. P., Westlye, L. T., Selbæk, G., Giegling, I., Hampel, H., Hiltunen, M., Levey, A. I., Andreassen, O. A., Rujescu, D., Jonsson, P. V., Bjornsson, S., Snaedal, J. and Stefansson, K. (2015) Loss-of-function variants in ABCA7 confer risk of Alzheimer's Disease. *Nature Genetics* 47, 445-447.
- Strittmatter, W. J., Weisgraber, K. H., Huang, D. Y., Dong, L. M., Salvesen, G. S., Pericak-Vance, M., Schmechel, D., Saunders, A. M., Goldgaber, D. and Roses, A. D. (1993) Binding of human apolipoprotein E to synthetic amyloid beta peptide: isoform-specific effects and implications for late-onset Alzheimer Disease. *Proceedings of the National Academy of Sciences of the United States of America* **90**, 8098-8102.
- Takechi, R., Lam, V., Brook, E., Giles, C., Fimognari, N., Armin Mooranian, A., Al-Salami, H., Coulson, S. H., Nesbit, M. and Mamo J. C. L. (2017) Blood-brain barrier dysfunction precedes cognitive decline and neurodegeneration in diabetic insulin resistant mouse model: an implication for causal link. *Frontiers in Aging Neuroscience* 9, 399.
- Tanzi, R. E. (2012) The genetics of Alzheimer Disease. Cold Spring Harbor Perspectives in Medicine 2, a006296.
- Tao, Q. Q., Chen, Y. C. and Wu, Z. Y. (2019) The role of CD2AP in the pathogenesis of Alzheimer's Disease. Aging and Disease 10, 901-907.
- Tapiainen, V., Lavikainen, P., Koponen, M., Taipale, H., Tanskanen, A., Tiihonen, J., Hartikainen, S. and Tolppanen, A. M. (2020) The risk of head injuries associated with antipsychotic use among persons with Alzheimer's Disease. *Journal of the American Geriatrics Society* 68, 595-602.
- Tuveson, D. A., Ahearn, J. M., Matsumoto, A. K. and Fearon, D. T. (1991) Molecular interactions of complement receptors on B lymphocytes: a CR1/CR2 complex distinct from the CR2/CD19 complex. *Journal of Experimental Medicine* 173, 1083-1089.
- Ulrich, J., Ulland, T., Mahan, T. E., Nyström, S., Nilsson, K. P., Song, W. M., Zhou, Y., Reinartz, M., Choi, S., Jiang, H., Stewart, F. R., Anderson, E., Wang, Y. Colonna, M. and Holtzman, D. M. (2018) ApoE facilitates the microglial response to amyloid plaque pathology. *Journal of Experimental Medicine* **215**, 1047-1058.
- Van Acker, Z. P., Bretou, M. and Annaert, W. (2019) Endo-lysosomal dysregulations and late-onset Alzheimer's Disease: impact of genetic risk factors. *Molecular Neurodegeneration* 14, 20.
- Van Eldik, L. J., Carrillo, M. C., Cole, P. E., Feuerbach, D., Greenberg, B. D., Hendrix, J. A., Kennedy, M., Kozauer, N., Margolin, R. A., Molinuevo, J. L., Mueller, R., Ransohoff, R. M., Wilcock, D. M., Bain, L. and Bales K. (2016) The roles of inflammation and immune mechanisms in Alzheimer's Disease. *Alzheimer's and Dementia* 2, 99-109.
- Vehmas, A. K., Kawas, C. H., Stewart, W. F. and Troncoso, J. C. (2003) Immune reactive cells in senile plaques and cognitive decline in Alzheimer's Disease. *Neurobiology of Aging* 24, 321-331.
- Velazquez, P., Cribbs, D. H., Poulos, T. L., Tenner, A. J. (1997) Aspartate residue 7 in amyloid beta-protein is critical for classical complement pathway activation: implications for Alzheimer's Disease pathogenesis. *Nature Medicine* 3, 77-79.
- Vishnu, V. Y., Modi, M., Sharma, S., Mohanty, M., Goyal, M. K., Lal, V., Khandelwal, N., Mittal, B. R. and Prabhakar, S. (2016) Role of plasma clusterin in Alzheimer's Disease-a pilot study in a tertiary hospital in northern India. *PLoS One* **11**, e0166369.
- Vitek, M. P., Brown, C. M. and Coltona C. A. (2009) APOE genotypespecific differences in the innate immune response. *Neurobiology of Aging* 30, 1350-1360.

Vogels, T., Murgoci, A. N. and Hromádka, T. (2019) Intersection of patho-

logical tau and microglia at the synapse. Acta Neuropathologica Communications 7, 109.

- Wadhwani, A. R., Affaneh, A., Van Gulden, S. and Kessler, J. A. (2019) Neuronal apolipoprotein E4 increases cell death and phosphorylated tau release in Alzheimer Disease. *Annals of Neurology* 85, 726-739.
- Weinstein, G., Beiser, A. S., Preis, S. R., Courchesne, P., Chouraki, V., Levy, D. and Seshadri, S. (2016) Plasma clusterin levels and risk of dementia, Alzheimer's Disease, and stroke. *Alzheimer's and Dementia* (*Amst*) **3**, 103-109.
- Whitmer, R. A., Gunderson, E. P., Barrett-Connor, E., Quesenberry, C. P., Jr. and Yaffe, K. (2005) Obesity in middle age and future risk of dementia: a 27-year longitudinal population based study. *BMJ* 330, 1360.
- Wijsman, E. M., Pankratz, N. D., Choi, Y., Rothstein, J. H., Faber, K. M., Cheng, R., Lee, J. H., Bird, T. D., Bennett, D. A., Diaz-Arrastia, R., Goate, A. M., Farlow, M., Ghetti, B., Sweet, R. A., Foroud, T. M. and Mayeux, R. and NIA-LOAD/NCRAD Family Study Group. (2011) Genome-wide association of familial late-onset Alzheimer's Disease replicates BIN1 and CLU and nominates CUGBP2 in interaction with APOE. *PLOS Genetics* 7, e1001308.
- Wojtas, A. M., Kang, S. S., Olley, B. M., Gatherer, M., Shinohara, M., Lozano, P. A., Liu, C. C., Kurti, A., Baker, K. E., Dickson, D. W., Yue, M., Petrucelli, L., Bu, G., Carare, R. O. and Fryer, J. D. (2017) *Proceedings of the National Academy of Sciences of the United States* of America 114, E6962-E6971.
- Wyss-Coray, T., Yan, F., Lin, A. H., Lambris, J. D., Alexander, J. J., Quigg, R. J. and Masliah, E. (2002) Prominent neurodegeneration and increased plaque formation in complement-inhibited Alzheimer's mice. *Proceedings of the National Academy of Sciences of the United States* of America **99**, 10837-10842.
- Xie, Z., Harris-White, M. E., Wals, P. A., Frautschy, S. A., Finch, C. E. and Morgan, T. E. (2005) Apolipoprotein J (clusterin) activates rodent microglia *in vivo* and *in vitro*. *Journal of Neurochemistry* **93**, 1038-1046.
- Yeh, F. L., Wang, Y., Tom, I., Gonzalez, L., C. and Sheng, M. (2016) TREM2 Binds to apolipoproteins, including APOE and CLU/APOJ, and thereby facilitates uptake of amyloid-beta by microglia. *Neuron* 91, 328-340.
- Yu, J. H., Han, K., Park, S., Cho, H., Lee, D. Y., Kim, J. W., Seo, J. A., Kim, S. G., Baik, S. H., Park, Y. G., Choi, K. M., Kim, S. M. and Kim, N. H. (2020) Incidence and risk factors for dementia in type 2 diabetes mellitus: a nationwide population-based study in Korea. *Diabetes and Metabolism Journal* 44, 113-124.
- Zenaro, E., Pietronigro, E., Della Bianca, V., Piacentino, G., Marongiu, L., Budui, S., Turano, E., Rossi, B., Angiari, S., Dusi, S., Montresor, A., Carlucci, T., Nanì, S., Tosadori, G., Calciano, L., Catalucci, D., Berton, G., Bonetti, B. and Constantin, G. (2015) Neutrophils promote Alzheimer's Disease-like pathology and cognitive decline via LFA-1 integrin. *Nature Medicine* 21, 880-886.
- Zhang, S., Zhang, D., Jiang, Y., Wu, L., Shang, H., Liu, J., Feng, R., Liao, M., Zhang, L., Liu, Y., Liu, G. and Li, K. (2015) CLU rs2279590 polymorphism contributes to Alzheimer's Disease susceptibility in Caucasian and Asian populations. *Journal of Neural Transmission (Vienna)* 122, 433-439.
- Zhao, L. (2019) CD33 in Alzheimer's Disease biology, pathogenesis, and therapeutics: a mini-review. *Gerontology* **65**, 323-331.
- Zhou, Z., Liang, Y., Zhang, X., Xu, J., Lin, J., Zhang, R., Kang, K., Liu, C., Zhao, C. and Zhao, M. (2020) Low-density lipoprotein cholesterol and Alzheimer's Disease: a systematic review and meta-analysis. *Frontiers* in Aging Neuroscience 12, 5.
- Zuccolo, J., Bau, J., Childs, S. J., Goss, G. G., Sensen, C. W. and Deans, J. P. (2010) Phylogenetic analysis of the MS4A and TMEM176 gene families. *PLoS One* 5, e9369.