Research Article

Alzheimer's Disease: APP, Gamma Secretase, APOE, CLU, CR1, PICALM, ABCA7, BIN1, CD2AP, CD33, EPHA1, and MS4A2, and Their Relationships with Herpes Simplex, C. Pneumoniae, Other Suspect Pathogens, and the Immune System

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Alzheimer’s disease susceptibility genes, APP and gamma-secretase, are involved in the herpes simplex life cycle, and that of other suspect pathogens (C. pneumoniae, H. pylori, C. neoformans, B. burgdorferi, P. gingivalis) or immune defence. Such pathogens promote beta-amyloid deposition and tau phosphorylation and may thus be causative agents, whose effects are conditioned by genes. The antimicrobial effects of beta-amyloid, the localisation of APP/gamma-secretase in immunocompetent dendritic cells, and gamma secretase cleavage of numerous pathogen receptors suggest that this network is concerned with pathogen disposal, effects which may be abrogated by the presence of beta-amyloid autoantibodies in the elderly. These autoantibodies, as well as those to nerve growth factor and tau, also observed in Alzheimer’s disease, may well be antibodies to pathogens, due to homology between human autoantigens and pathogen proteins. NGF or tau antibodies promote beta-amyloid deposition, neurofibrillary tangles, or cholinergic neuronal loss, and, with other autoantibodies, such as anti-ATPase, are potential agents of destruction, whose formation is dictated by sequence homology between pathogen and human proteins, and thus by pathogen strain and human genes. Pathogen elimination in the ageing population and removal of culpable autoantibodies might reduce the incidence and offer hope for a cure in this affliction.

1. Introduction

Hundreds of genes have been implicated in Alzheimer’s disease, many of which can be grouped into discrete signalling networks and pathways relevant to the various sub-pathologies, risk factors, and biochemistry of Alzheimer’s disease. Many of the environmental risk factors associated with Alzheimer’s disease, including infectious agents (herpes simplex, chlamydia pneumonia, and Borrelia burgdorferi) as well as Vitamin A deficiency, hypercholesterolaemia, hyperhomocystinaemia or folate deficiency, oestrogen depletion, cerebral nerve growth factor (NGF) deprivation, diabetes, cerebral hypoperfusion (leading to hypoxia and hypoglycaemia) or are able to promote cerebral beta-amyloid deposition (in the absence of any particular gene variant) in animal models [1]. KEGG pathway and other analyses of the multiple genes implicated in Alzheimer’s disease have shown that subsets of susceptibility genes can be grouped into networks that are relevant to each of these amyloidogenic pathways (e.g., bacterial and viral entry pathways [1, 2], cholesterol/lipoprotein function [3, 4], growth factor signalling [5], folate and homocysteine pathways [6], insulin signalling [7], and steroid or Vitamin A metabolism [8, 9]). A large number of genes are also related to the immune network [10] (see http://www.polygenicpathways.co.uk/algkegg.htm and a recent review for further details [1]). These gene subsets are thus related to multiple external factors that are each able to promote beta-amyloid deposition, suggesting that certain genes are related to the causes of Alzheimer’s disease, (agents able to provoke beta-amyloid deposition) rather than (and as well as) to the underlying pathology of the disease itself.

Several studies have implicated the herpes simplex virus in the aetiology of Alzheimer’s disease [11–13]. Viral DNA is found in amyloid plaques [14], which are also heavily
enriched in proteins used by the virus during its life cycle, as well as in proteins related to the immune network [15], and Immunoglobulin IgM, but not IgG seropositivity for herpes simplex is predictive of the subsequent development of Alzheimer’s disease [16]. IgM seropositivity is indicative of viral reactivation which again can be induced by several of the risk factors relevant to Alzheimer’s disease and its underlying genetic pathways (e.g., NGF deprivation, 17-beta oestradiol, hypoxia, or fever and interleukin 6 activation, with the latter being common and general consequences of infection [1]).

Along with herpes simplex, a number of other pathogens have been implicated in Alzheimer’s disease and its associated pathologies. The viral, bacterial, spirochete, and fungal pathogens implicated in dementia or Alzheimer’s disease are referenced at (http://www.polygenicpathways.co.uk/alzenrisk.htm) and include HHV-6, Chlamydia pneumoniae, Helicobacter pylori, periodontal pathogens involved in gum disease [17], Borrelia burgdorferi, and Cryptococcus neoformans. HIV-1 is also able to provoke dementia with Alzheimer’s disease pathology [18]. Of these, H. pylori eradication has been reported to improve performance and increase lifespan in Alzheimer’s disease patients [19], while two case reports indicated virtually complete recovery from long-term (3 years) misdiagnosed dementia/Alzheimer’s disease following antifungal treatment for C. neoformans infection [20, 21]. Many of these pathogens including herpes simplex, HHV-6, C. Pneumoniae, H. pylori and the periodontal pathogen, P. Gingivalis, have also been implicated in atherosclerosis [22–25], while C. neoformans infection in rabbits induces an increase in neutrophil superoxide production, plasma lipid peroxidation, and an increase in inflammatory cells, forerunners of atherosclerosis [26]. Atherosclerosis of the carotid arteries, or of the circle of Willis and leptomeningeal arteries, is a significant predictor of risk in dementia or Alzheimer’s disease and correlates with Alzheimer’s disease pathology [27, 28]. Cerebral hypoperfusion (hypoglycaemia, hypoxia, ischaemia, or carotid occlusion) or other factors linked to atherosclerosis (e.g., high cholesterol or homocysteine levels) are also able, per se, to induce cerebral beta-amyloid deposition in animal models (see above).

Genomewide association studies (GWAS) have now identified a subset of genes which, along with APOE4 [29], contribute a high proportion of genetic risk. These include clusterin (CLU), phosphatidylinositol-binding clathrin assembly protein (PICALM) and complement receptor 1 (CR1) as well as the ATP cassette transporter ABCA7, Bridging integrator BIN1, a CD2-associated protein (CD2AP), CD33, ephrin A1 (EPHA1), and a membrane-spanning 4-domains, subfamily A (MS4A) cluster recently honed down to MS4A2, although other genes within this cluster may also be relevant [30, 31].

As discussed below, the major Alzheimer’s disease genes implicated by the recent GWAS data, as well as APP and gamma secretase, and previous GWAS results are majoritarily involved in pathogen entry and defence, particularly in relation to herpes simplex, but also to other relevant pathogens, and in the immune network. This suggests that genes, pathogens, and the immune system act together to cause Alzheimer’s disease, and that a focus on pathogen detection and elimination should be a priority in the ageing at risk population.

2. Methods

The genes identified in a number of recent genomewide association studies are available at the GWAS repository at the National Human Genome Research Institute http://www.genome.gov/gwastudies/ [32] and, along with pre-GWAS genes and environmental risk factors, at http://www.polygenicpathways.co.uk/alzenrisk.htm. The genes returned from very large sample sets (N > 10,000) include ABCA7, APOE, BIN1, CD2AP, CD33, CLU, CR1, EPHA1, MS4A2, MS4A4A, MS4A4E, MS4A6A, and PICALM whose pro perties in relation to diverse pathogens were identified by literature survey. While it is recognised that such genes, particularly APOE, ABCA7, CR1, and clusterin, which are involved in lipoprotein function and/or amyloid processing (see below), may exert effects on other relevant branches of Alzheimer’s disease pathophysiology, the focus of this paper is on pathogens and the immune system, which appear to be the common factors integrating this network. Throughout the text, these and other genes implicated in Alzheimer’s disease from the GWAS and pre-GWAS era are highlighted in bold and appended to the various processes in which they are involved (derived from a KEGG pathway analysis of these genes http://www.polygenicpathways.co.uk/alzkegg.htm). Herpes simplex binding proteins, and key interactors, currently numbering over 450, are stocked and referenced at http://www.polygenicpathways.co.uk/herpeshost.html. KEGG pathway analysis of this interactome is provided at http://www.polygenicpathways.co.uk//HERPESKEGG.htm. Expression data are provided in Figure 1 and are also hyperlinked to the BioGPS webserver http://www.biogps.gnf.org/, which provides general gene information and mRNA expression profiles for most human genes, based on custom arrays from 79 human issues [33, 34]. Predicted B-cell epitopes from human beta-amyloid (1–42), nerve growth factor (NP_002497.2), or the microtubule protein, tau (NP_001116538.2) were identified using the BepiPred server http://www.cbs.dtu.dk/services/BepiPred/ [35] and their sequences compared with pathogen proteomes (Borrelia burgdorferi, C. neoformans, Helicobacter pylori, herpes viruses HSV-1, HSV-2, HHV-6, and the cytomegalovirus (HHV-5)) using the NCBI BLAST server (Protein versus protein: BlastP) [36].

3. Results

3.1. The Complement System (ABCA7, CR1, CLU, CD2AP, and Beta-Amyloid) Figure 2. Complement receptor 1 (highly expressed in myeloid CD33+ cells (bone marrow) http://www.biogps.org/#goto=genereport&tid=1378/) is a receptor for herpessimplex, adenovirus 5, the influenza virus and HIV-1, as well as for a number of other pathogens, including P. gingivalis, C. neoformans, Streptococcus pneumoniae, Staphylococcus aureus, and the malaria parasite,
Figure 1: Continued.
Figure 1: The mRNA distribution of the major genes derived from GWAS in Alzheimer’s disease, as well as that of APP and gamma-secretase components. Data are from the BioGps website.
**Figure 2:** Portions of the complement cascade in relation to beta-amyloid processing: Alzheimer’s disease susceptibility genes returned from very large genomewide association studies are in black, and those from the pre-GWAS era in grey. Binding interactions are indicated by linked diamonds and other effects by arrows. C. Neo: *Cryptococcus neoformans*; C. Pneu: *chlamydia pneumoniae*; H. Pyl: *Helicobacter pylori*; P. Ging: *Porphyromonas gingivalis*; C1–C9: complement components. MAC: membrane attack complex. P-choline: phosphatidylcholine; black star: Herpes simplex: see text for details.

*Plasmodium falciparum* [37–43] and is a general clearance receptor for complement opsonised pathogens [44]. Clusterin, predominantly expressed in brain, liver, and testis, (http://www.biogps.org/#goto=genereport&id=1191/) is a ligand for the lipoprotein receptor, megalin (LRP2) that is involved in beta-amyloid clearance, and also a complement inhibitor that prevents the formation of the membrane attack complex, a channel that is inserted into pathogen membranes, killing them by lysis [45]. This complex is also seen in Alzheimer’s disease neurones [46, 47]. The herpes simplex virus interacts with other members of the complement cascade, by binding to the complement component and CR1 ligand, C3 and its derivatives and to CD59, a further inhibitor of the formation of the membrane attack complex (see review) [48]. C. pneumoniae interacts with this pathway by binding to properdin (CFP), a protein that stabilises the complement C3 and C5 convertase and contributes to the formation of the membrane attack complex [49]. CD59 is also incorporated into chlamydial inclusion bodies [50]. Complement component C3 binds to melanins derived from *C. neoformans* [51] and cryptococcal capsules bind to C3 and activate the alternative complement pathway [52]. Complement component C3 also binds to the bacterial surface of *H. pylori*, and the complement pathway is involved in bactericidal effects against this pathogen [53]. *P. gingivalis* also uses complement receptor 3 (an integrin complex of integrin, alpha M/integrin, beta 2 (ITGAM/ITGB2)) for entry [54], and herpes simplex glycoprotein C also binds to this complex [55] as does *C. neoformans* [56], while ITGB2 is involved in *C. pneumoniae* entry in human coronary artery endothelial cells [57]. This macrophage complement receptor, also known as MAC-1, generally mediates the phagocytosis of pathogens coated with complement C3 derivatives [58]. T. C3 also binds to *P. gingivalis* although the pathogen has devised an elegant escape strategy involving digestion of complement components C3, C4, and C5 by bacterial secreted proteases, known as gingipains [59].

The complement inhibitor CD59 is also a ligand for CD2, and CD59 activation of this receptor, presumably involving CD2AP, activates T cell receptor signalling resulting in the secretion of interleukins (IL1A, IL2 and IL6) and granulocyte macrophage colony stimulating factor (CSF2) [60, 61].

*ABCA7* plays a role in the complement-mediated activation of phagocytosis in macrophages. Complement component C1q, which binds to IgM or IgG complexed antigens (relevant to most pathogens), binds to macrophage calreticulin and LRP1 and C1q binding to macrophages markedly increased the expression of both LRP1 and ABCA7, effects
which enhance the phagocytic abilities of macrophages [62]. C1q also binds to complement receptor CR1, an effect involved in the immune clearance of opsonised pathogens [63]. C1q also binds to beta-amyloid and is involved in amyloid-related complement activation [64].

3.2. Clathrin-Mediated Endocytosis (BIN1, CLU, CD2AP, PICALM) Figure 3. Mammalian surface receptors are endocytosed, via clathrin-dependent or independent processes (KEGG: ADRB1, ADRB2, BIN1, CAV1, CD2AP, CLU, DNM2, HLA-A, HSP A1B, LDLR, NTRK1, PICALM) and either recycled or tagged for destruction by the ubiquitin/proteasome system (KEGG: UBD, UBE2I UBQLN1, UCHL1) or by lysosomes (KEGG: ABCA2, ARSA, ARSB, CTSD, CTSS, NPC1, NPC2, LIPA). Early endosomes receive traffic from the cell surface, which is transferred to late endosomes for traffic to lysosomes. Late endosomes also receive traffic from the trans-Golgi network used to synthesise trafficking proteins, which are transferred to late endosomes for recycling to lysosomes. Late endosomes also receive traffic from the trans-Golgi network used to synthesise trafficking proteins, which are transferred to late endosomes for recycling to lysosomes.

Endosomal traffic moves along the microtubule (GSK3B, MAPT, TTL7) or actin/myosin (MYH8, MYH13) networks via dynein/dynactin (DM2, DNMBP) or kinesin (KIF18B, KIF20B, KNS2), related motors and Rho GTPases, and vacuolar sorting proteins (SOFCS1, SOFCS2, SOFCS3, SORL1) inter alia [65]. These processes are usurped by many viruses and other pathogens to gain access to cells and to various intracellular compartments, while the lysosomal or proteasomal pathways may be used to destroy pathogen proteins [66].

Clathrin-mediated endocytosis is one of several processes used by *Helicobacter pylori*, herpes simplex, and many other viral, bacterial and fungal pathogens to gain entry to cells [67–69].

PICALM, expressed primarily in myeloid and dendritic cells of the immune network http://www.biogps.org/#!goto=genereport&id=8301/, plays a key role in clathrin-related endocytosis, binding to clathrin heavy chains (CLTC and CLTC1), and recruiting the clathrin and adaptor protein 2 (AP-2) to the plasma membrane. The AP-2 complex is a heterotetramer consisting of permutations of two large adaptins (alpha (AP2A1, AP2A2)) or beta (AP2B1), a medium adaptin (AP1M1, AP1M2), and a small adaptin (sigma AP2S1).

PICALM controls the endocytosis of the cation-independent mannose-6-phosphate IGF2 receptor (IGF2R) [70], one used by Herpes simplex for entry and cell-to-cell transmission [71] and by *C. pneumoniae* for cellular entry [57]. IGF2R is also a component of late endosomes disrupted by the *Helicobacter pylori* VacA cytotoxin [72]. The mannose-6-phosphate receptor binds to clusterin. PICALM also binds to a nuclear exportin crm-1 (XPO1) used by the herpes simplex virus during its life cycle [48].

Gamma-adaptins (GGA, GGA2, GGA3) bind to clathrins and mannose-6-phosphate receptors and regulate protein
traffic between the Golgi network and the lysosome and the sorting of mannose-6-phosphate receptors (IGF2R and M6PR) at the trans-Golgi network [73]. This network is also related to important Alzheimer’s disease susceptibility genes as the interactions culled from NCBI gene show that GGA1 binds to the sortilin-related receptor, SORL1, and the APP cleaving beta-secretase BACE2, while GGA2 binds to the beta-secretases BACE1 and BACE2, SORL1 and the prolyl-isomerase PIN1.

CD2AP, primarily expressed in dendritic cells and B lymphoblasts http://www.biogps.org/#goto=generereport&gid=23607/, is a scaffolding molecule that regulates the actin cytoskeleton and is primarily associated with the T-lymphocyte marker protein CD2. CD2 stimulates T cell activation and is involved in the creation of contacts between antigen presenting cells and T cells (the immunological synapse), effects mediated via CD2AP and clathrin [74]. CD2AP is also involved in the entry of the helicobacter vacuolating toxin VacA and connects the actin cytoskeleton to early endosomes containing VacA [75]. CD2 is cleaved by gingipain proteases from P. gingivalis [76].

CD2AP also binds to the actin-bonding protein, cortactin (CTTN), a protein that is exploited by several bacteria (Escherichia coli, Shigella, Neisseria, Rickettsia, Chlamydia, Staphylococcus, Cryptosporidium, and Helicobacter pylori), fungi (Candida Albicans), and viruses (Vaccinia) enabling them to modify the actin cytoskeleton, which they use for transport [77–79]. CD2AP has not been specifically associated with herpes simplex, although the actin cytoskeleton is exploited by this and many other viruses [80].

CD2AP also associated with E-Cadherin, (CDH1) [81]. The ectodomain of E-cadherin is involved in bacterial adherence to mammalian cells [82]. E-Cadherin binds to the H. pylori toxin CagA [83] and is also cleaved by the Helicobacter pylori protein HtRA allowing the pathogen to invade the intracellular compartment [84]. CDH1 and CDH5 expressions are increased by C. pneumoniae infection of human brain microvascular endothelial cells, contributing to vascular permeability changes and atherosclerosis [85].

Bridging integrator 1 (BIN1), also known as amphi- physin 2, is primarily expressed in the pineal and skeletal muscle, or otherwise ubiquitously http://www.biogps.org/#goto=generereport&gid=274/. It is also involved in the clathrin-mediated endocytosis machinery [86] and binds to dynamin that regulate the clathrin network [87] including DNM1 and the herpes simplex binding partner DNM2 [88] and to clathrins and the alpha adaptins, AP2A1 and AP2A2 [89]. BIN1 also participates in phagocytosis in macrophages and is associated, but only transiently, with early phagosomes; however, it is retained on vacuoles containing Chlamydia pneumoniae, an effect that reduces the ability of the macrophage system to kill the bacteria via nitric oxide generation. Macrophages expressing a dominant negative BIN1 internalise C. pneumoniae, but do not allow their killing [90]. BIN1 also binds to a number of alpha integrins (ITGA1, ITGA3, and ITGA6) [91]: integrins are used for attachment by many viruses, bacteria, and fungi and may serve as pattern recognition receptors regulating the immune response [92]. Individual integrins bind to many others, forming heteromeric complexes; for example, ITGA1 binds to ITGA3 or ITGA6, while ITGA3 binds to ITGB1 (a receptor for the H. pylori protein CagA [93]), ITGB4, or ITGB5, and ITGA6 binds to ITGB1 and ITGB4 (data from NCBI gene).

3.3. The Immune Network (APOE, BIN1, CD2AP, CD33, MS4A2) (Figure 4). CD33, mainly expressed in myeloid cells, monocytes, and dendritic cells (http://www.biogps.org/#goto=generereport&gid=945/), is a member of the sialic acid binding Immunoglobulin g-like lectin (SIGLEC) family. CD33-related SIGLECs regulate adaptive immune responses and are also important as macrophage pattern recognition receptors for sialylated pathogens, including enveloped viruses [94]. CD33 binds to alpha2-3- or alpha2-6-linked sialic acids (N-acetyl neuraminic acid) [95]. These particular sialic acids are expressed on the surface envelope glycoproteins (B, D, and H) of the herpes simplex virion, and these residues are required for viral entry into cells [96]. N-acetyl neuraminic acid is expressed by C. neoformans, is involved in fungal adhesion to macrophages [97], and is also a component of the cell wall of B. burgdorferi [98], while Helicobacter pylori adhesins also bind to this particular form of sialic acid [99, 100] as does P. gingivalis [101].

BIN1, as well as its relationship to the clathrin mediated endocytosis machinery, also regulates the expression of indoleamine 2,3-dioxygenase (IDO1), an enzyme that catalyzes the first rate-limiting step in tryptophan metabolism to N-formyl-kyurenine [102]. IDO1 upregulation is an important defence mechanism against pathogenic bacteria, many of which are unable to synthesise tryptophan. Their survival is compromised by the diversion of tryptophan metabolism to kynurenines [103]. This IDO1 response is also deleterious to other pathogens and parasites, including T. gondii, and to a number of viruses, including herpes simplex and other herpes viruses [104]. IDO1 protein expression is localised to plaques and tangles in the Alzheimer’s disease brain. IDO1 activation can lead to the production of toxic tryptophan derivatives such as 3-hydroxyanthranilic acid or the N-methyl-D aspartate receptor agonist and excitatory neurotoxin, quinolinic acid [105] (GRIN2B, GRIN3A). Plasma tryptophan levels are also lower in the ageing population and in Alzheimer’s disease, a pattern accompanied by immune activation, and by increased concentrations of quinolinic acid [106, 107].

MS4A2, expressed mainly in the tonsils, lymph nodes, B cells, and dendritic cells http://www.biogps.org/#goto=generereport&gid=931/, is a component of the immunoglobulin E (IgE) receptor, which is involved in allergic responses in which allergens bound to receptor bind IgE result in the activation of allergic mediators such as histamine [108]. Mice immunised with inactivated herpes simplex develop IgE-specific antibodies to the virus [109]. High levels of IgE are also observed in man following recurrent herpes simplex infection [110] and human IgE antibodies are also known to interact with herpes family viruses including HSV-1 and 2 and the Epstein-Barr and cytomegalovirus [111] and also to C. pneumoniae, H. pylori, and B. burgdorferi.
Figure 4: Immune-related genes: Alzheimer’s disease susceptibility genes returned from very large genomewide association studies are in black, and those from the pre-GWAS era in grey. Binding interactions are indicated by linked diamonds and other effects by arrows.

Borr: Borrelia burgdorferi; C. Pneu: chlamydia pneumoniae; Cytomeg: cytomegalovirus; H. Pyl: Helicobacter pylori; P. Ging: Porphyromonas gingivalis; IgE: immunoglobulin E, Sialic: alpha2-3- or alpha2-6-linked sialic acids: the genes in the top right square were returned from GWAS prior to the very large studies. black star: Herpes simplex: see text for details.

[112–115]. IgE-related allergic responses are also involved in C. neoformans infection [116]. Other members of this gene cluster (including MS4A4A, MS4A4E, and MS4A6A) are also structurally related to the immunoglobulin E receptor and to CD20 (MS4A1) and also regulate B cell and T cell proliferation and/or differentiation [117, 118].

**EPHA1** is an ephrin receptor, primarily expressed in the liver and otherwise ubiquitously (http://www.biogps.org/#goto=gene-report&id=2041/). Only three protein/protein interactions for EPHA1 are reported in the NCBI gene interaction section, including its ligand EFNA1, the anaplastic lymphoma receptor tyrosine kinase (ALK), and a SMAD-specific E3 ubiquitin protein ligase 2 (SMURF2). EFNA1 is one of several proteins identified as being important in the entry of C. pneumoniae into human coronary artery endothelial cells [57]. SMURF2 is known to bind to the VP22 tegument protein of herpes simplex [119] and plays a role in clathrin-mediated endocytosis and the subsequent ubiquitin-related proteasomal degradation of TGF beta receptors, to which it binds [120].

**Clusterin** is a ligand for TGF beta receptors (TGFBR1/TGFBR2) [121]. TGF beta signalling exerts immunosuppressive effects and inhibits host immunosurveillance and the recruitment of immunocompetent cells by chemokines [122]. ALK is ubiquitously expressed (http://www.biogps.org/#goto=gene-report&id=238/). It plays a role in neural development, and its expression decreases with age [123]. ALK is best characterised via its relationship with lymphomas, caused by ALK gene fusion with any of several other housekeeping genes [124]. Its key involvement in lymphoma suggests a role in the immune network although the function of the normal ALK protein is poorly understood.

3.4. Lipoprotein Related (APOE, ABCA7, CLU) (Figures 2 and 5). **ABCA7** is an ATP-binding cassette transporter, predominantly localised in the pineal gland and cells of the immune network (T cells, natural killer cells, and dendritic cells http://www.biogps.org/#goto=gene-report&id=10347/). The lipoproteins APOA1 and APOE are substrates for ABCA7, and in cultured HEK-293 cells, plasma membrane-situated ABCA7 increases the efflux of phosphatidylcholine and sphingomyelin efﬂux to APOA1 and APOE, with no effect on cholesterol efﬂux [125]. However, cholesterol efﬂux to lipiddaden ABCA7, but not to lipid free APOE, is increased by ABCA7 expression in HEK-293 cells [126]. Sphingomyelin is enriched in extracellular herpes simplex viral membranes: this sphingomyelin, together with phosphatidylserine, is collected by the viral envelope during viral passage from the nuclear membrane to the exocytosis pathway [127]. Herpes viral infection leads to an increased incorporation of phosphate into membrane sphingomyelin of the host [128]. Inhibition of sphingomyelinase has also been shown to markedly reduce herpes simplex viral reproduction [129]
and also inhibits the antifungal effects of neutrophils against *C. neoformans* infection. Sphingomyelin is a receptor for the Helicobacter toxin VacA [130] and is also incorporated into inclusion bodies in *C. pneumoniae*-infected cells [131]. Phosphatidylcholine plays an important role in the fusion of herpes simplex glycoproteins B and H with the host cell lipid membrane, a process used in viral entry [132]. Phosphatidylcholine is also able to trigger capsular enlargement in *C. neoformans* infection [133].

**ABC7** expression increases the extracellular surface deposition of ceramide (derived from sphingomyelin) [134]. Ceramide, a potent activator of apoptosis, as well as its downstream target, caspase 3 (CASP3) are both able to reactivate the herpes simplex virus from latency [135]. Ceramide is also incorporated into *C. pneumoniae* inclusions, an effect that may play a role in the antiapoptotic effects of this bacterium [136]. **APOA1** exerts antiviral effects against herpes simplex and inhibits viral entry into cells as well as viral-induced cell fusion and intercellular spread [137]. In macrophages, **ABC7** is expressed intracellularly and does not participate in cholesterol or phospholipid efflux, instead playing a role in the phagocytosis of apoptotic cells, an important general defence mechanism against invading pathogens [62, 138].

### 3.4.1. Apolipoprotein E

Possession of the **APOE4** allele facilitates the entry and transmission of herpes simplex in mice models [139]. In man, **APOE** is also involved in hepatitis C, HIV-1, and herpes simplex infectivity [140–143], and **APOE4** facilitates the binding of *C. pneumoniae* elementary bodies to host cells [144].

**APOE** mRNA is primarily expressed in the liver, adipocytes; kidney and brain, with very low expression in the peripheral immune network (http://www.biogps.org/gateway#id=348/) but nevertheless plays an important role in the immune system. For example, the presence of the **APOE4** allele is associated with an enhanced macrophage inflammatory response, and cytokine responses to the intracerebral injection of lipopolysaccharide are increased in **APOE4** transgenic mice, which also exhibit increased microglial activation. The anti-inflammatory effects of 17-beta-estriadiol on microglia are also reduced in such animals [145, 146]. C-reactive protein (**CRP**) levels are also decreased in **APOE4** carriers [145–147]. **CRP** is an acute phase protein that binds to phosphocholine on dead or dying cells and on bacteria, subsequently activating the complement pathway [148]. Resistance to infection (*Klebsiella pneumoniae*) or endotoxaemia is also decreased in **APOE4** knockout mice [149].

In addition, atherosclerosis is induced or worsened by infection with a number of relevant pathogens (*Cytomegalovirus*, herpes simplex, *Helicobacter pylori*, influenza, *C. pneumoniae* or *P. gingivalis*) in **APOE** knockout mice [150–156]. *Helicobacter pylori* is able to promote atherosclerosis in heterozygous **APOE (+/−)** LDLR (+/−) mice, which is associated with an immune response to the bacterial heat shock protein hsp60 [157].

### 3.5. Other GWAS Genes (Figure 4)

Prior to the very large GWAS collaboration, several other genes had been identified in smaller genomewide studies (**APOC1**, **CELF2**, **DISC1**, **FAM113B**, **GAB2**, **MTHFD1L**, **PAX2**, **PCDH11X**, **PVR2** **RFC3**, **SASH1**, **TOMM40**, **TTLL7**, and **ZNF224**). **PVR2** is a receptor for herpes simplex (*HSV-1 and HSV-2*) [158], and the mitochondrial translocator, **TOMM40**, a receptor for certain chlamydial species [159]. The replication factor **RFC3** is part of a complex necessary for human DNA polymerase activity, a process exploited by many viruses including herpes simplex, whose virion component ICP34.5 binds to phosphocholine on dead or dying cells and on bacteria, subsequently activating the complement pathway [148]. Resistance to infection (*Klebsiella pneumoniae*) or endotoxaemia is also decreased in **APOE4** knockout mice [149].

**CRP** is an acute phase protein that binds to phosphocholine on dead or dying cells and on bacteria, subsequently activating the complement pathway [148]. Resistance to infection (*Klebsiella pneumoniae*) or endotoxaemia is also decreased in **APOE4** knockout mice [149].

**DISC1** is a component of the microtubule-associated dynein motor complex used in viral traffic [163]; **TTLL7** (tubulin tyrosine ligase-like family, member 7) also regulates tubulin phosphorylation [164] and can again be related to viral traffic along the microtubule network (see below). **CELF2** (also known as **CUGBP2**) is a member of the **APOBEC1** cytidine deaminase mRNA editing complex that also controls herpes simplex viral replication [165]. **GAB2**
is a member of the GRB2-associated binding protein family which act as adapter hubs transmitting signalling via cytokine and growth factor receptors, and T- and B-cell antigen receptors (definition from NCBI gene), while PAX2 inhibits the expression of the antimicrobial peptide beta defensin (DEFB1) [166], a gene associated with HSV-1 and cytomegalovirus seropositivity in children with acute lymphoblastic leukaemia [167], as well as with *H. pylori* or chlamydial infections [168, 169], also endowed with antimicrobial activity against *C. neoformans* and other pathogens [170]. MTHD1L (methylene-tetrahydrofolate dehydrogenase (NADP+ dependent) 1-like) is involved in the mitochondrial synthesis of tetrahydrofolate which in turn is important in the de novo synthesis of purines and thymidate and in the regeneration of methionine from homocysteine (definition from NCBI gene). Many pathogens, including herpes simplex, express thymidylate kinases, which are important for viral replication and a target for acyclovir [171]. Hyperhomocysteinaemia correlates with *C. pneumoniae* homocysteinaemia and is also associated with *H. pylori* infection in the context of atherosclerosis [173]. The apolipoprotein APOC1 is a component of high-density lipoprotein: herpes simplex is present in all lipoprotein blood fractions in blood (VLDL, LDL and HDL) and the lipid component of these lipoproteins binds to viral glycoprotein B [174] (c.f. APOA1, APOA4, APOA5, APOC1, APOC2, APOC3, APOC4, APOD, and APOE). No immediately apparent pathogen-relevant interactions were found for FAM113B (expressed exclusively in T cells, dendritic cells, and natural killer cells http://www.biogps.org/#goto?genereport&id=91523/), PCDH11X (which is ubiquitously expressed http://www.biogps.org/#goto?genereport&id=27328/), or SASH1 (primarily expressed in the brain and lung although also in other tissues, including the immune network http://www.biogps.org/#goto?genereport&id=23328/) although the pathogen/immune theme is clearly carried through, particularly in relation to herpes simplex, in this second rank of Alzheimer’s disease susceptibility genes.

3.6. Beta Amyloidosis (Figure 2). APOE, *clusterin*, and **complement receptor 1** play key roles in beta-amyloid clearance as do two further herpes simplex binding proteins APOA1, and alpha-2 macroglobulin (A2M). This is primarily mediated via lipoprotein receptors. A2M, or APOE-bound Aβ, is cleared by the lipoprotein receptor LRP1, while LRP2 (megalin) clears clusterin-bound Aβ. LRP8 is a receptor for both APOE and *clusterin*. APOA1 is also involved in beta-amyloid clearance via its transporter ABCA1. The role of ABCA7 has not been examined, although APOA1 is also a ligand for this transporter (see above). The Varicella Zoster and herpes simplex glycoprotein E binding protein, *insulin-degrading enzyme*, are also involved in beta-amyloid degradation, as is caspase-3 which is activated by the herpes simplex viral US3 kinase. The HSV-1 binding protein, complement C3 is also a ligand for LRP1 and LRP8, both of which play a role in C3 cellular uptake. Beta amyloid in the bloodstream is processed by its binding to complement C3, which subsequently binds to **complement receptor 1** on erythrocytes. The effects above are referenced in a recent review [48].

Clathrin-dependent endocytosis is also involved in the internalisation and recycling of neuronal **APP**, a procedure necessary for the subsequent cleavage of **APP** and the generation of beta-amyloid [175, 176], and in the neuronal [177], but not the microglial uptake of both soluble and aggregated beta-amyloids, the latter representing an important rout of disposal [178]. However, while knockdown of the clathrin assembly protein AP180 in a neuronal cell line does reduce beta-amyloid generation, **PICALM** knockdown does not [179]. The accumulation of beta-amyloid in the brain interstitial space, related to the prior endocytosis of **APP**, is clathrin dependent [180]. Clathrin-mediated endocytosis is relevant to many receptors, including members of the lipoprotein family (LRP1, LRP2, LRP8, LDLR, VLDLR) [181], all of which are involved in beta-amyloid clearance, as well as in cholesterol and lipoprotein physiology [182].

**ABCA7** plays a role in beta-amyloid secretion, which is increased in Chinese hamster ovary cells expressing **APP** and **ABCA7**. This was related to an effect on **APP** intracellular retention, rather than on secretase-mediated proteolysis of **APP** [126].

**Gamma-secretase** cleaves **APP**, and other gamma-secretase substrates also play key roles in **APP** processing (ADAM10) [183], lipid and cholesterol function (LRP1, LDLR, VLDLR), and other processes relevant to Alzheimer’s disease, for example, NOTCH signalling [184].

No other immediately apparent relationships with beta-amyloid could be found by literature survey for CD2AP, CD33, and **EPHA1** or for **MS4A**-related proteins, although such are not precluded.

3.6.1. The Microtubule Network and Tau Phosphorylation. Many pathogens, including herpes simplex, *helicobacter, chlamydiae, P. gingivalis*, and *C. neoformans* [185–188], use the microtubule network that serves as a useful railway track between various cellular compartments, and may hijack dynnein and kinesin motors for this purpose (see http://www.polygenicpathways.co.uk/herpeshost.html for herpes simplex). **Tau** (MAPT) stabilises microtubules by interacting with tubulins and promoting microtubule assembly [189]. When **tau** is phosphorylated, by any of several kinases, microtubules become disorganised. **Tau** hyperphosphorylation and neurofibrillary tangles are among the core pathologies of Alzheimer’s disease [190] and can be promoted by herpes simplex infection [191]. In relation to viral/human protein homology, herpes simplex proteins are homologous to a number of kinases known to phosphorylate **tau** (GSK3A, GSK3B, MAPK1, and CAMK2B) suggesting that **tau** phosphorylation could be a direct result of a viral kinase [192].

3.6.2. **APP** and Gamma Secretase. **APP** plays a key role in the herpes simplex life cycle and is involved in its intracellular transport [193], an effect likely related to the ability of both **APP** and the herpes simplex protein, US11, to bind to the **APP** and kinesin binding protein APPBP2 (also known as pat1) [194, 195].
The AntiMicrobial Effects of Beta-Amyloid. Beta-amyloid is an antimicrobial peptide with broad spectrum activity against a variety of yeasts and bacteria, effects that were attenuated by anti-Aβ antibodies [196]. Beta-amyloid also has antiviral effects and, like acyclovir, attenuates the stimulatory effects of herpes simplex on miRNA-146a levels in neuronal cells [197]. Beta-amyloid also activates innate immune responses via the activation of pattern recognition receptors, such as Toll receptors (TLR2, TLR4), which are also involved in beta-amyloid clearance [198, 199]. The antimicrobial, antiviral, and immunostimulant properties of beta amyloid are, however, likely to be abrogated by the presence of beta-amyloid autoantibodies in the sera of the ageing population and in Alzheimer’s disease [200]. As immunogenic regions of beta-amyloid are homologous to similar regions within proteins expressed by all of the principal pathogens discussed in this paper, such antibodies are likely to be derived from antibodies raised to numerous pathogens (see below).

**Gamma Secretase: Localisation to Dendritic Cells and Cleavage of Pathogen Receptors.** **Gamma secretase** is constituted of four components: the presenilins (PSEN1 or PSEN2), anterior-oropharynx-defective-1 (APH1A), the Presenilin enhancer-2 (PSENEN), and nicastrin (NCSTN) [201]. While all components are expressed in cerebral tissue, the major focus of distribution is within cells of the immune network: dendritic cells, myeloid cells, and monocytes for PSEN1 [http://www.biogps.org/goto?genereport&id=5663], dendritic cells and natural killer cells for PSEN2 [http://www.biogps.org/goto?genereport&id=55851], dendritic cells and myeloid cells for nicastrin [http://www.biogps.org/goto?genereport&id=23385] and B cells, dendritic cells, natural killer cells, and myeloid cells for APH1A. The substrate, APP, is the only gene in this set that appears to be preferentially distributed in brain compartments, but, as with **gamma-secretase** components, it is also highly expressed in dendritic cells of the immune system [http://www.biogps.org/goto?genereport&id=351]. The primary function of such cells is to process antigens and present them to B cells and T cells. They scout for and recognise pathogens via the agency of numerous pattern recognition receptors, for example, Toll receptors (TLR2, TLR4), or viral DNA sensors, expressed on their surface [202, 203].

As well as cleaving APP, **gamma secretase** is involved in the proteolysis of at least three herpes simplex receptors, nectin 1 alpha (PVRL1) [204], and syndecans (SDC1, SDC2) [205]. SDC1 is also a receptor for HIV-1, Hepatitis E, and the human papillomavirus [206–209], while SDC3, also a **gamma secretase** substrate, is an HIV-1 and papillomavirus receptor [210, 211].

Several other **gamma secretase** substrates (reviewed by Lleó and Saura [201]) also function as viral/pathogen receptors, including ADAM10, a receptor for the cytotoxin Staphylococcus aureus alpha-haemolysin [212], CD44, an entry receptor for C. neoforms [213], CD46, a receptor for adenoviruses, measles virus, human herpes virus 6 (HHV-6), Streptococci, and Neisseria [214]: CD46 is also cleaved by a protease secreted by P. gingivalis [215]. Desmoglein-2 is an adenovirus receptor [216], while rhinovirus receptors include the lipoprotein receptors LDLR, VLDLR [217, 218]. LDLR is also a hepatitis C receptor [219]. NOTCH1 and NOTCH4 are activated by the Epstein-Barr virus [220, 221], while ERBB4 is a receptor for vaccinia and other pox viruses [222]. The low affinity nerve growth factor (NGFR) is a rabies virus receptor, [223], Ephrin B2, (EfnB2) a Nipah virus and Hendra virus receptor [224] and sialaphorin (SPN), a receptor for the influenza A, and both human and simian immunodeficiency viruses [225, 226] and for the C. neoforms virulence factor, galactoxylomannan [227]. Fractalkine (CX3CL1) binds to the cytomegalovirus chemokine receptor, US28 [228], while the chemokine CXCL16 is a scavenger receptor for phosphatidylserine and oxidized low density lipoprotein [229]: phosphatidylserine is the major lipid membrane component in most bacteria [230]. Dystroglycan is a receptor for the Lymphocytic choriomeningitis and Lassa fever viruses [231, 232] and also for mycobacterium leprae (the Leprosy pathogen) [233].

The antimicrobial and immunostimulant effects of beta-amyloid, the cleavage of a number of pathogen receptors by **gamma secretase**, and the concentration of both APP and **gamma-secretase** components in dendritic cells suggest that a major function of this key group, implicated in both familial and late onset Alzheimer’s disease, is dedicated to pathogen defence, and that increased beta-amyloid generation is primarily a defence mechanism to rid the body (and brain) of invading pathogens: This scenario is supported by the ability of herpes simplex, C. pneumoniae, and B. burgdorferi to increase beta-amyloid deposition [234–236]. One might expect many other pathogens to increase beta-amyloid deposition, and that, as has been noted in atherosclerosis, (a component of Alzheimer’s disease pathology), the final extent of risk may depend upon the overall pathogen burden, rather than upon any specific pathogen [237].

3.6.3. Autoantibodies Derived from Pathogens as Contributory Causative Agents. Viruses and bacteria express proteins containing short contiguous amino acid stretches (pentapeptides or more, or longer gapped consensii) that are identical to those in human proteins: these pathogen/human consensi number in millions and concern all human proteins [238–241].

Autoantibodies, which are observed in many, if not most human diseases, are often regarded as an epiphenomenon of little consequence. However, they can traverse the blood brain barrier [242] (which is compromised in Alzheimer’s disease [243]) and are also able to enter cells, essentially by hitching a ride on viruses, via high affinity IgG receptors (Fc gamma receptors) (FCER1G) in the case of the rhinovirus, or the SARS coronavirus, or via the tripartite motif protein, TRIM21, in the case of adenoviruses, where they are able to activate an intracellular immune attack. It would appear that the cellular entry of antibody laden viruses is diverted from their usually preferred receptors towards those used by antibodies [244–246]. This may be relevant to the MS4A family. Fc gamma receptors are localised in microglia and
astrocytes in the brain and their expression is upregulated by blood brain barrier disruption [247], while TRIM21 appears to be exclusively localised in peripheral immunocompetent cells (http://www.biogps.org/#goto=genereport&id=6737).

This ability places autoantibodies in a rather more sinister context, as their targeting of extracellular and intracellular human proteins would be expected to effect protein knockdown, a strictly immunopharmacological effect, as well as immune attack.

In multiple sclerosis, schizophrenia, and cystic fibrosis, as well as in Alzheimer’s disease, numerous autoantigens targeted by the autoantibodies reported in these conditions, contain peptide sequences identical to those in the pathogens also implicated in the disease. Such regions of homology are focalised within epitope regions of the human autoantigen [192, 248–250]. In Parkinson’s disease, antibodies to the Epstein-Barr virus, which has been implicated in postencephalitic adult and juvenile Parkinsonism, are also known to cross-react with synuclein, a key protein involved in neurodegeneration in this disorder [251–253]. In addition, 22 autoantigens reported in HIV-1/AIDS contain HIV-1/human matching sequences [254], supporting the contention that autoantibodies are in many cases antibodies initially raised to pathogens, which because of this homology, then target their human homologues. It has been argued that slightly dissimilar, rather than exact matches, are the more malignant in terms of autoimmunity, being less likely to be regarded as self, while the antibodies would retain low affinity for human counterparts [254, 255].

Autoantibody production would also be sustained, even after pathogen elimination, by continued encounter of the human homologue. The production of autoantibodies must be dependent upon the extent of pathogen/human matching, and thus by genes which determine human protein sequences. These pathogen/human matches are also highly and significantly enriched in the products of susceptibility genes implicated in Alzheimer’s disease, multiple sclerosis, and schizophrenia [192, 248, 250]. Many genes related to Alzheimer’s disease, including those described above, are involved in the immune network [10, 256], and the propensity for developing autoantibodies to particular proteins is also genetically determined and inherited [257]. Thus, despite the fact that all human proteins likely possess pathogen homologues, whether or not autoantibodies will be produced will depend on the extent of human/pathogen matching (determined by human genes and the strain of pathogen encountered), on whether the pathogen protein is deemed as self or nonself (a factor determined soon after birth) and on other genetic factors related to the immune network, and autoimmunity. Somatic hypermutation, that drives the creation of multiple antibodies and which selects against those reacting to self, is disrupted in autoimmune disorders [258]. These links suggest an interplay, applicable to many diseases, where susceptibility gene products, risk promoting pathogens and autoimmunity can all be related via protein sequence homology.

It has also been noted that autoantigens have a tendency to relate to proteins known to bind to dermatan sulphate, a component of dead cells [259] and a constituent of glycosaminoglycan receptors for many bacteria and viruses [260].

3.6.4. Sequence Comparisons: Beta-Amyloid, NGF, and Tau versus Pathogen Proteins. All three of these proteins are autoantigens in Alzheimer’s disease and were chosen for analysis because of the ability of their antibodies to promote features of Alzheimer’s disease, in vivo. In mice, immunisation with neuronal tau produces neurofibrillary tangle-like structures, axonal damage, and gliosis, as in Alzheimer’s disease [261]. In addition, in transgenic mice, initially expressing NGF antibodies only in lymphocytes, NGF antibodies subsequently enter the brain provoking extensive cortical degeneration, cholinergic neuronal loss, tau hyperphosphorylation, and beta-amyloid deposition [262]. Beta-amyloid autoantibodies are also able to promote meningoencephalitis, both in laboratory models and in clinical trials [263, 264]. Beta-amyloid plaques contain numerous inflammatory proteins, and even without meningoencephalitis, these are commonly found within the walls of meningeal and medium-sized cortical arteries in Alzheimer’s disease [265].

Almost the entire length of the tau protein (638/776 amino acids = 82.2%) was predicted as immunogenic (B cell epitope), as defined by the server set cutoff index of 0.35. For the analysis in Table 1, only regions of the tau protein with an immunogenicity index >2.5 were examined for homology. For other proteins (NGF and beta-amyloid), the analysis concerned immunogenic regions above the cutoff value of 0.35.

All pathogens express proteins with homology to each autoantigen, specifically within predicted B-cell epitope regions of the human autoantigen (Table 1), suggesting that antibodies raised to any could be responsible for targeting these human proteins, under the appropriate circumstances. Perversely, the successful elimination of the pathogen via antibody production could set in motion the very autoimmune responses that may be crucial to the development of Alzheimer’s disease, a Pyrrhic victory, which would also be promulgated by any further encounter with these very common pathogens, or by structurally related proteins from other pathogens, as well as by continual encounter of the human autoantigen homologue (see Section 3.6.5).

As well as autoantibodies to these three proteins, a number of autoantibodies targeting highly relevant proteins have been reported in Alzheimer’s disease. These have functional effects on their target proteins and include antibodies that block the activity of ATP synthase, induce apoptosis, and increase the cellular uptake of high density lipoprotein [266, 267], antibodies to cholinergic neurones that cause immunalysis of brain synaptosomes [268], antibrain antibodies that enhance intraneuronal beta-amyloid deposition [269] as well as antibodies to the nicotinic receptor CHRNA7, that displace its ligand alpha-bungarotoxin [270]: autoantibodies to the receptor for advanced glycation products (AGER) [271], to the antimicrobial peptide SI00B, have also been reported [272].

3.6.5. Population Genetics: Susceptibility Genes Related to the Cause of the Disease, rather than to the Disease Itself. Using
Table 1: Viral, bacterial, and fungal protein homology with beta-amyloid (top), NGF (middle), or tau (bottom); Predicted B cell epitope segments were compared with Borrelia burgdorferi, C. neoformans, C. pneumoniae, H. pylori, P. gingivalis and herpes viruses (HSV1, HHV6, and cytomegalovirus) proteomes by BLAST analysis. The B cell antigenicity indices are shown, and those above the server set threshold of 0.35 are in italics. The first column shows the amino acid number within the peptide or protein sequence, and the second shows the amino acid pertaining to that position. The alignments with pathogen proteins are shown. Spaces represent nonidentical amino acids and + signs amino acids with similar physicochemical properties. Only highly antigenic regions of pentapeptides or more were processed. The VGGVV sequence, antibodies to which label beta-amyloid in brain tissue, despite relatively low antigenicity, has already been reported to be identical to proteins expressed by 69 viruses including HSV-1, HSV-2, and HHV6.

| Position B-Amy | Amino acid | B-cell index | Alignments |
|----------------|------------|--------------|------------|
| 1              | D          | 0.41         | C. neoformans +AE HDSSG+ Borrelia burgdorferi DAE F H+SG EV H. pylori DA FRD HSV-1 +AE RH HHV-6 D FR DS P. gingivalis +AEFR C. pneumoniae DA EFRHD and +AEFR +SG |
| 2              | A          | 0.35         | C. neoformans AEFR D GY+V H. pylori AEF D S YE and AE+RH+ Borrelia burgdorferi AEF H+ Cytomegalovirus AEFR HD HSV-1 AE R SG HHV-6 AE+ HD P. gingivalis A+H S+ and AEFR C. pneumoniae AE DSG |
| 3              | E          | 0.62         | H. pylori EFRHD HHV-6 EF DSG Borrelia Burgdorferi EFR DS C. neoformans EF R DS YE P. gingivalis E R DSG Y V C. pneumoniae EF SGYEV |
| 4              | F          | 0.73         | C. neoformans FRHDS Borrelia burgdorferi +RH SGY++ and F H+SG H. pylori F HD EV Cytomegalovirus FR SGY P. gingivalis +RHDS C. pneumoniae F H+SGY |
| 5              | R          | 0.85         | C. neoformans R D GYEV H. pylori RHDS Y V and R SGYE Borrelia burgdorferi RH+ GY Cytomegalovirus RHD YE and RHDSG HSV-1 RH SG HHV-6 RHDS P. gingivalis R+DS Y+ |
| 6              | H          | 0.57         | C. neoformans HDSSG Y H. pylori F+ +DSGY and HD G EV and HD EV Borrelia burgdorferi H+SG Y+V HSV-1 HDSP G. pylori HDSSG C. pneumoniae +++SGY+V |
| 7              | D          | 0.69         | C. neoformans DSGY +V H. pylori +SG+EV HSV-1 DSGY P. gingivalis DSG +EV C. pneumoniae DSGY V |
| 8              | S          | 0.38         | P. gingivalis SGYEV H. pylori SGYE C. neoformans SGY++ C. pneumoniae SG+EV |
| 9              | G          | 0.63         | H. pylori GYE V Borrelia burgdorferi GYE V KL+ C. neoformans GYE LV and GY++ +LV P. gingivalis GYEV C. pneumoniae GYEV and GY HH |
| 10             | Y          | 0.56         | H. pylori YE HH and YE+ HQ and Y+++H Q and YE HHH Cytomegalovirus YE V Borrelia Burgdorferi YE+ KL C. neoformans YE +Q FC P. gingivalis Y++H K C. pneumoniae Y+V +Q LV |
| 11             | E          | 0.58         | H. pylori EV +Q Cytomegalovirus EV HQ I Borrelia Burgdorferi EV +KL C. neoformans EV Q LV P. gingivalis EV KLV C. pneumoniae EV KLV |
| 12             | V          | 0.35         | H. pylori +H Q Cytomegalovirus V HQ LV HHV-6 VH QK+V Borrelia Burgdorferi VH KL C. neoformans +HH LV P. gingivalis VH +LV C. pneumoniae V HQK |
| 13             | H          | −0.17        | H. pylori and C. pneumoniae HHQK Cytomegalovirus HH KL P. gingivalis HH KL |
| 14             | H          | −0.66        | Borrelia Burgdorferi HQKL+ C. pneumoniae and HSV1 HQKL P. gingivalis +QKLV |
| 15             | Q          | −1.03        | C. neoformans and P. gingivalis and C. pneumoniae QKLV |
| 16             | K          | −1.47        | H. pylori: Cryptococcus neoformans Borrelia burgdorferi Chlamydotophila pneumoniae KL/VF Human herpesvirus 1 KL/VF |
| 17             | L          | −1.34        | Human herpesvirus 5: Human herpesvirus 6 LVFF |
| 18             | V          | −1.20        |
| 19             | F          | −0.93        |
| 20             | F          | −0.98        |
| 21             | A          | −0.82        |
| 22             | E          | −0.31        |
| 23             | D          | 0.23         |
| 24             | V          | 0.81         | Borrelia burgdorferi Cryptococcus neoformans Porphyromonas gingivalis VGSKN Cytomegalovirus +SNK Helicobacter pylori Chlamydotophila pneumoniae VGSN |
| 25             | G          | 1.24         | H. pylori Chlamydotophila pneumoniae SNK |
| 26             | S          | 1.22         |
| 27             | N          | 0.90         |
| 28             | K          | 0.36         |
### (a) Continued.

| Position | Amino acid | B-cell index | Alignments |
|----------|------------|--------------|------------|
| 29       | G          | 0.30         |            |
| 30       | A          | −0.24        |            |
| 31       | I          | −0.58        |            |
| 32       | I          | −1.00        |            |
| 33       | G          | −1.14        |            |
| 34       | L          | −1.19        |            |
| 35       | M          | −1.23        |            |
| 36       | V          | −1.16        | 69 viruses/phages VGGVV |
| 37       | G          | −0.97        |            |
| 38       | G          | −1.02        |            |
| 39       | V          | −0.63        |            |
| 40       | V          | −0.45        |            |
| 41       | I          | −0.80        |            |
| 42       | A          | −1.06        |            |

### (b)

| NGF position | Amino acid | B-cell index | Alignment |
|--------------|------------|--------------|-----------|
| 18           | A          | 0.59         | *C. neoformans* AEPHS |
| 19           | E          | 1.16         | *P. gingivalis* EPHSES—NVP Cytomegalovirus EPHS+S |
| 20           | P          | 1.32         | *C. neoformans* P+S NVPA and PHS +P SESNV |
| 21           | H          | 1.78         | *Borrelia burgdorferi* HSES VP and HSES N H +P+ |
|              |            |              | *C. neoformans* S+SNVP T P *Borrelia burgdorferi burgdorferi C. neoformans* |
| 22           | S          | 1.64         | *Chlamydia pneumoniae P. gingivalis SESNV P. gingivalis* S+SNVP C. *pneumoniae* SESNV A |
| 23           | E          | 1.68         | *C. neoformans* ESNVP and ESNV AG |
| 24           | S          | 1.51         | *C. neoformans* SNVP |
| 25           | N          | 1.61         | *C. neoformans* Cytomegalovirus *P. gingivalis* NVPA *C. neoformans* NV TIPQA *P. gingivalis* +VPAG HT |
| 26           | V          | 1.45         | *C. neoformans* P. gingivalis VPAGH *C. neoformans* VP AGHT *C. neoformans* VPAG TI and V AGHT+ |
| 27           | P          | 1.36         | *C. neoformans* HSV-1 PAGHT *C. neoformans* PAGHT P *C. neoformans* PAG TIP |
| 28           | A          | 1.04         | *C. neoformans* H. pylori AGHTI *C. neoformans* AG H IPQA and AGHT PQ and AGHT+P and AG TIP HSV-1 HSV-1 AGQ PQ and AGHT QA |
| 29           | G          | 1.00         | *C. neoformans* GHTI Q and GHT PQ and G TIPQ |
| 30           | H          | 0.93         | *C. pneumoniae HTI QA C. neoformans* HT PQ Q and HTIP A |
| 31           | T          | 1.05         | *C. neoformans* P. gingivalis TIPQA |
| 32           | I          | 0.95         |            |
| 33           | P          | 0.64         |            |
| 34           | Q          | 0.41         |            |
| 35           | A          | 0.46         |            |
| 51           | A          | 0.38         | *C. neoformans* AR SAPA and AR APAA and A SAPAA and ARSA AA and ARSAP A and ARS PAA and AR—SAPAA |
| 52           | R          | 0.54         | *HSV-1 RSAPAA Borrelia burgdorferi burgdorferi RSA AA* |
| 53           | S          | 0.91         | *C. neoformans* C. *pneumoniae* Cytomegalovirus HSV-1 HSV-2 *P. gingivalis* SAPAA |
| 54           | A          | 0.89         |            |
| 55           | P          | 0.72         |            |
| 56           | A          | 0.69         |            |
| 57           | A          | 0.53         |            |
| 64           | A          | 0.46         | *C. neoformans* AG TRNI and AGQT RN and AGQ TR P. *gingivalis* AGQTR |
| 65           | G          | 0.59         | *C. neoformans* + RNITV and GQTRN |
| NGF position | Amino acid | B-cell index | Alignment |
|--------------|------------|--------------|-----------|
| 66           | Q          | 0.42         | P. gingivalis Borrelia burgdorferi QTRNI Cytomegalovirus QTRN—IT |
| 67           | T          | 0.43         | C. neoformans P. gingivalis TRNIT |
| 68           | R          | 0.49         | C. neoformans RNIT DP and RNITV |
| 69           | N          | 0.76         | C. neoformans C. pneumoniae H. pylori NITVD |
| 70           | I          | 0.66         | |
| 71           | T          | 0.56         | |
| 90           | S          | 0.40         | C. neoformans STQPR and STQPP AA and STQPP EA C. pneumoniae STQ PRE C. pneumoniae Cytomegalovirus STQPP HSV-1 STQ PR |
| 91           | T          | 0.63         | C. neoformans TQP REA and TQPPR |
| 92           | Q          | 1.06         | C. neoformans QPPRE |
| 93           | P          | 1.49         | C. neoformans PP REAA C Neoformans P. gingivalis PPREA |
| 94           | P          | 1.91         | C. neoformans HSV-2 H. pylori PREAA |
| 95           | R          | 2.13         | Borrelia burgdorferi burgdorferi C. neoformans AA TQD Borrelia burgdorferi burgdorferi P. gingivalis AAD QD HSV-2 AADT D HHV-6 AAD +DL C. neoformans AADT D and AA TQD and A DTQD and AADTQ and AADT+ D+D P. gingivalis ADTQ L H. pylori AADTQ |
| 96           | E          | 2.13         | Borrelia burgdorferi ADT DLD C. neoformans AD QDLD and AD QDL P. gingivalis ADT DL and AD QDL H. pylori TQDL |
| 97           | A          | 1.92         | Borrelia burgdorferi burgdorferi C. neoformans AA TQD Borrelia burgdorferi Burgdorferi C. neoformans AAD QD HSV-2 AADT D HHV-6 AAD +DL C. neoformans AADT D and AA TQD and A DTQD and AADTQ and AADT+ D+D P. gingivalis ADTQ L H. pylori AADTQ |
| 98           | A          | 1.92         | Borrelia burgdorferi ADT DLD C. neoformans AD QDLD and AD QDL P. gingivalis ADT DL and AD QDL H. pylori TQDL |
| 99           | D          | 1.39         | C. neoformans DT DLD and D QDLD C. pneumoniae DTQDL |
| 100          | T          | 1.25         | C. neoformans H. pylori P. gingivalis TQDLD |
| 101          | Q          | 0.66         | Borrelia burgdorferi burgdorferi C. neoformans H. pylori P. gingivalis QDLD H. pylori QD DFEV |
| 102          | D          | 0.73         | Borrelia burgdorferi burgdorferi C. neoformans H. pylori DLD C. neoformans DLD EVG and DLD VG |
| 103          | L          | 0.54         | C. neoformans LD EVGG and LDFE GG and LDFEV and LDF VG C. pneumoniae HSV-1 HSV-2 L+ EVGG |
| 104          | D          | 0.45         | Borrelia burgdorferi burgdorferi DFEVG C. neoformans DF VGGA and D EVGG |
| 105          | F          | 0.42         | C. neoformans FEVGG Cytomegalovirus FE GGAA |
| 106          | E          | 0.49         | C. neoformans EVGGAA and EVGG P and EVGA and E+GGAAP H. pylori EVGG Borrelia burgdorferi burgdorferi E+GA GF+ P. gingivalis VGGAAP and VGGAA C. neoformans VGGAA PF and VGGAA NR and VGGAA and VG GAAP C. pneumoniae VGGAA AP H. pylori VG GAAP and VGG APF and VGGAA P. gingivalis VGGAA |
| 107          | V          | 0.39         | |
| 108          | G          | 0.74         | C. neoformans C. pneumoniae HSV-2 GGAAP |
| 109          | G          | 0.44         | C. neoformans GA APFN T and GAAPF |
| 110          | A          | 0.95         | C. pneumoniae AAPFN Borrelia burgdorferi AAP+NR HSV-1 AAP RT |
| 111          | A          | 0.83         | C. neoformans APFN T RS C. neoformans H. pylori APFN TH C. pneumoniae AP N RT R RSS |
| 112          | P          | 0.99         | C. neoformans PFNRT and PF RTH Borrelia burgdorferi burgdorferi PF NRT |
| 113          | F          | 0.84         | C. neoformans FNRT SKR |
| 114          | N          | 0.75         | C. neoformans NR RSKRS S and NRT R RSKS Cytomegalovirus N T RSKRS |
| 115          | R          | 0.63         | C. neoformans RT R SKRS and RTHRS Borrelia burgdorferi burgdorferi RTHRS |
| 116          | T          | 0.63         | C. neoformans THRS RS and THR SK |
| 117          | H          | 0.64         | C. neoformans HRS RSS and HRSKR C. Pneumonie HRSKR |
### (b) Continued.

| NGF position | Amino acid | B-cell index | Alignment |
|--------------|------------|--------------|-----------|
| 118          | R          | 0.94         | C. neoformans RSRRS and RS RSSS and RS KRSS and RS KRSS and RSK SSS and RSKRS S P. gingivalis RSKR S and RSKRS Borrelia burgdorferi burgdorferi RSKRS |
| 119          | S          | 0.88         | C. neoformans SKRSS and SKRSS C. pneumoniae H. pylori HSV-1 HSV-2 SKRSS |
| 120          | K          | 1.12         | C. neoformans Cytomegalovirus HHV-6 H. pylori KRSSS |
| 121          | R          | 1.13         | |
| 122          | S          | 1.12         | |
| 123          | S          | 0.83         | |
| 124          | S          | 0.50         | |
| 144          | G          | 0.52         | C. neoformans GDKTTA and GDKT |
| 145          | D          | 0.54         | H. pylori DK TATDI Borrelia burgdorferi burgdorferi C. neoformans C. pneumoniae H. pylori DKTA HSV-1 +KTT TD |
| 146          | K          | 0.84         | CF. Pneumoniae KTTAT+ C. neoformans H. pylori KTTAT |
| 147          | T          | 1.27         | C. neoformans HSV-1 TTATDI C. neoformans P. gingivalis TTATD |
| 148          | T          | 1.22         | C. neoformans TATDIK Borrelia burgdorferi burgdorferi C. neoformans C. pneumoniae H. pylori TATDI |
| 149          | A          | 1.21         | C. neoformans HHV-6 HHV-6B P. gingivalis ATDIK |
| 150          | T          | 1.08         | |
| 151          | D          | 1.01         | |
| 152          | I          | 0.97         | |
| 153          | K          | 0.61         | |
| 179          | C          | 0.87         | C. neoformans CR PNPV C. pneumoniae CRDPN P+ S RGI |
| 180          | R          | 1.40         | C. pneumoniae RDPNPV Borrelia burgdorferi burgdorferi RD NP VDS C. neoformans RDP PVDS and RDPNPV+ and RDPNPV HHV-6 HHV-6B RDPNPV HSV-1 HSV-2 RDPNPV V |
| 181          | D          | 1.36         | Borrelia burgdorferi burgdorferi D NPVD and DPN VD C. neoformans DPNPV and DP PVDS and DP PVDS and DPN VDS C. pneumoniae DPNV HSV-1 DPNPV S HSV-2 +P PVDS |
| 182          | P          | 1.69         | C. neoformans PN VDSG and PNP DSG and PNPV P. gingivalis PNPV+S and P PVDS |
| 183          | N          | 1.72         | H. pylori NPVD G |
| 184          | P          | 1.85         | C. neoformans PV DSGCR and P PVDS RG and PVDSG Cytomagalovirus P DSG RGI P. gingivalis PV DSGC |
| 185          | V          | 1.74         | HSV-2 VDSG RG HSV-1 +DSG RG C. neoformans VDSG R |
| 186          | D          | 1.51         | C. neoformans DSGC GI and DSG RG |
| 187          | S          | 1.28         | Borrelia burgdorferi burgdorferi C. neoformans SGCRG and SG RGI and S CRGI |
| 188          | G          | 0.79         | C. neoformans GC IDSKH W and GCRG D P. gingivalis GCRGI and GCRG+ |
| 189          | C          | 0.79         | P. gingivalis CRGID C. neoformans C GIDS |
| 190          | R          | 0.85         | C. neoformans R IDS K and RGIDS and RGID K H. pylori RGIDS HSV-1 HSV-2 RG+DS H. pylori RG DSK Borrelia burgdorferi burgdorferi RGID K |
| 191          | G          | 0.65         | C. neoformans GIDS HW and GIDSK and GIDS H Borrelia burgdorferi burgdorferi H. pylori P. gingivalis GIDSK P. gingivalis GID KH and G DSKH H. pylori GI SKH |
| 192          | I          | 0.60         | Borrelia burgdorferi burgdorferi IDSKH C. neoformans P. gingivalis IDS K |
| 193          | D          | 0.3          | C. neoformans DSKH W Borrelia burgdorferi burgdorferi DSK WN |
| 194          | S          | 0.40         | C. neoformans SKHW+ |
| 195          | K          | 0.44         | |
| 197          | W          | 0.41         | |
| 212          | T          | 0.33         | C. neoformans TMDGKQ and TMDGK |
| 213          | M          | 0.31         | P. gingivalis MDGKQ |
| 214          | D          | 0.39         | C. neoformans DGKQA and DGKQA C. pneumoniae DGK AA |
| NGF position | Amino acid | B-cell index | Alignment                        |
|--------------|------------|--------------|----------------------------------|
| 215          | G          | 0.48         | C. neoformans GKQAA              |
| 216          | K          | 0.53         |                                  |
| 217          | Q          | 0.45         |                                  |

| Tau position | Amino acid | B-cell index | Alignment                                                                 |
|--------------|------------|--------------|---------------------------------------------------------------------------|
| 53           | E          | 2.516        | C. neoformans (GSK3)EDGSEEP S and E+G EEPG and +DGS+EP S and ED GSEE GS   |
|              |            |              | and EDGS++ GS and EDGSE and +D EEPG and EDG S PGS Cytomegalovirus EDG EEP |
|              |            |              | and +DG EE and ED GSEE P. gingivalis EDGSEE and E+G SEEP and EDGS EE      |
|              |            |              | HHV-6 HHV-6B EDGS EE C. pneumoniae E GSEE Borrelia burgdorferi E GSEE     |
| 54           | D          | 2.568        | C. neoformans DGSEEP and DGS+EPG and DGSEE P. gingivalis DGS EPG and      |
|              |            |              | DGSEE and DGS EP and DGSE EP and DGSE P Cytomegalovirus DS EP and DG EE  |
|              |            |              | G C. pneumoniae DGSE GS and +G EE GS Borrelia burgdorferi DGSE+ P.        |
|              |            |              | gINGIVALIS +GSEE                                                          |
| 55           | G          | 2.621        | C. neoformans GSEEP and G EEPE and G +EPGS and GS EEPG and GSEE GS        |
|              |            |              | Cytomegalovirus GS+EP S P. gingivalis GS EPG H. pylori GSEE G C.          |
|              |            |              | pneumoniae GSEE GS                                                      |
| 56           | S          | 2.732        | C. neoformans SEEPG and SEE GS and S EPGS and SEEP S C. pneumoniae SEEPG |
|              |            |              | and SEE GS and SE PGS P. gingivalis SEE GS and S EPGS                   |
| 57           | E          | 2.774        | C. neoformans EEPGS and +EPGS and EEPE E and EE GE C. pneumoniae EEPGS   |
|              |            |              | HSV-1 HSV-2 EEPG                                                        |
| 58           | E          | 2.678        | HHV-6 HHV-6B EPGSE C. neoformans EPGSE and EPGS+ P. gingivalis EPGS+     |
| 59           | P          | 2.564        | Borrelia burgdorferi SG GPED C. neoformans SG GPEDT and SGT PE and SGTGP |
| 60           | G          | 2.544        | and SG GPE and SGTG E and SG GP+ P. gingivalis SGTG E C. pneumoniae SGTG |
| 61           | S          | 2.556        | PE Cytomegalovirus SGTP+                                               |
| 62           | E          | 2.287        | C. neoformans GT PED and GTG ED and GTGPE and G GPED and GTGP D and G    |
|              |            |              | EDTE HSV-1 GTGPE and GTGP D and GTGP+D HSV-2 GTGPE D and G GPED C.        |
|              |            |              | pneumoniae GTGPE H. pylori GTGP D                                         |
| 171          | S          | 2.315        | HHV-6 TGPEDT and TG PEDT C. neoformans TG PEDT and TG EDT and T PEDT    |
| 172          | G          | 2.54         | TGPED C. pneumoniae TGPED H. pylori TG EDT Borrelia burgdorferi TGPE T+   |
| 173          | T          | 2.731        | C. neoformans GPEDT and GPED TE and GP DTE and GPED E HHV-6 HHV-6B      |
| 174          | G          | 2.709        | HG PEDT                                                                   |
| 175          | P          | 2.807        | C. neoformans H. pylori P. gingivalis PEDTE                              |
| 176          | E          | 2.7          |                                                                            |
| 177          | D          | 2.563        | HSV-1 SP DSPP and SPQ SP C. neoformans SPQDS and S QDSP and SP DSPP and  |
| 178          | T          | 2.397        | SP DSPP and SPQD PP and PQ DSPPS and SPQ PPSSK and SPQ SP and SP DSPP    |
| 179          | E          | 2.225        | and SP QDSP and SPQD PP and PQ DSPPS and P+DSPP and PQ S PPSSK           |
| 228          | S          | 2.396        | C. neoformans PQ SPPS and P DSPPS and PQDSP and PQ S PPSSK and PQ SPPPP  |
| 229          | P          | 2.744        | PQ and PQS and PQD PP and PQ DSPPS P. gingivalis PQDS P HSV-2 P DSPP      |
| 230          | Q          | 2.763        | HHV-6 PQ+PP and PQ PP K Borrelia burgdorferi PQ+ P SK                    |
| 231          | D          | 2.929        | C. neoformans QSPP and ++ PPSSK and QDSP PS and Q SPPS P. gingivalis QDSP |
| 232          | S          | 2.882        | C. neoformans SPQDS and S QDSP and SP DSPP and SP DSPP and SP QDSP and  |
|              |            |              | SP DSPP and SPQD PP and PQ DSPPS and PQ PPSSK and PQ S PPSSK and PQ SPPPP|
|              |            |              |                                                                            |
| Tau position | Amino acid | B-cell index | Alignment |
|--------------|------------|--------------|-----------|
| 233          | P          | 2.75         | C. neoformans DGRPP C. pneumoniae DG PPQ HSV-1 DG PPQ HSV-2 DGRPP C. neoformans GRPPQ |
| 234          | P          | 2.794        | DG PP+ Cytomegalovirus DG R PQ and DG PP and +GRPP Borrelia burgdorferi DG PP |
| 235          | S          | 2.68         | C. pneumoniae PGE P and P EGPE and PGEGP and PGEG EA and P EGPEA |
| 242          | D          | 2.387        | C. pneumoniae DGPP HSV-1 HHV-6 PG GPE P |
| 243          | G          | 2.49         | C. pneumoniae DGPPC. pneumoniae PGEGP EA and PG GPE C. pneumoniae PGE PEA and PGEGP H. pylori PG GPE HSV-1 HHV-6 PG GP A |
| 244          | R          | 2.56         | C. pneumoniae DGPP HSV-1 HHV-6 PG GPE P |
| 245          | P          | 2.42         | C. pneumoniae DGPPC. pneumoniae PGEGP EA and PG GPE C. pneumoniae PGE PEA and PGEGP H. pylori PG GPE HSV-1 HHV-6 PG GP A |
| 246          | P          | 2.164        | C. pneumoniae DGPPC. pneumoniae PGEGP EA and PG GPE C. pneumoniae PGE PEA and PGEGP H. pylori PG GPE HSV-1 HHV-6 PG GP A |
| 247          | Q          | 2.004        | C. pneumoniae DGPPC. pneumoniae PGEGP EA and PG GPE C. pneumoniae PGE PEA and PGEGP H. pylori PG GPE HSV-1 HHV-6 PG GP A |
| 331          | P          | 2.259        | C. pneumoniae DGPPC. pneumoniae PGEGP EA and PG GPE C. pneumoniae PGE PEA and PGEGP H. pylori PG GPE HSV-1 HHV-6 PG GP A |
| 332          | G          | 2.681        | C. pneumoniae DGPPC. pneumoniae PGEGP EA and PG GPE C. pneumoniae PGE PEA and PGEGP H. pylori PG GPE HSV-1 HHV-6 PG GP A |
| 333          | E          | 2.715        | C. pneumoniae DGPPC. pneumoniae PGEGP EA and PG GPE C. pneumoniae PGE PEA and PGEGP H. pylori PG GPE HSV-1 HHV-6 PG GP A |
| 334          | G          | 2.634        | C. pneumoniae DGPPC. pneumoniae PGEGP EA and PG GPE C. pneumoniae PGE PEA and PGEGP H. pylori PG GPE HSV-1 HHV-6 PG GP A |
| 335          | P          | 2.592        | C. pneumoniae DGPPC. pneumoniae PGEGP EA and PG GPE C. pneumoniae PGE PEA and PGEGP H. pylori PG GPE HSV-1 HHV-6 PG GP A |
| 336          | E          | 2.463        | C. pneumoniae DGPPC. pneumoniae PGEGP EA and PG GPE C. pneumoniae PGE PEA and PGEGP H. pylori PG GPE HSV-1 HHV-6 PG GP A |
| 337          | A          | 2.405        | C. pneumoniae DGPPC. pneumoniae PGEGP EA and PG GPE C. pneumoniae PGE PEA and PGEGP H. pylori PG GPE HSV-1 HHV-6 PG GP A |
| 414          | H          | 1.819        | C. pneumoniae DGPPC. pneumoniae PGEGP EA and PG GPE C. pneumoniae PGE PEA and PGEGP H. pylori PG GPE HSV-1 HHV-6 PG GP A |
| 415          | P          | 2.274        | HSV-1 HSV-2 HPTPG C. neoformans HPT GSS and HP PGSS and HPTP SS and HP P SS C. pneumoniae HP PGSS and +PT SS |
| 416          | T          | 2.503        | HSV-1 HSV-2 HPTPG C. neoformans HPT GSS and HP PGSS and HPTP SS and HP P SS C. pneumoniae HP PGSS and +PT SS |
| 417          | P          | 2.717        | HSV-1 HSV-2 HPTPG C. neoformans HPT GSS and HP PGSS and HPTP SS and HP P SS C. pneumoniae HP PGSS and +PT SS |
| 418          | G          | 2.469        | HSV-1 HSV-2 HPTPG C. neoformans HPT GSS and HP PGSS and HPTP SS and HP P SS C. pneumoniae HP PGSS and +PT SS |
| 419          | S          | 2.054        | HSV-1 HSV-2 HPTPG C. neoformans HPT GSS and HP PGSS and HPTP SS and HP P SS C. pneumoniae HP PGSS and +PT SS |
| 420          | S          | 1.76         | HSV-1 HSV-2 HPTPG C. neoformans HPT GSS and HP PGSS and HPTP SS and HP P SS C. pneumoniae HP PGSS and +PT SS |
| 493          | P          | 2.43         | HSV-1 HSV-2 HPTPG C. neoformans HPT GSS and HP PGSS and HPTP SS and HP P SS C. pneumoniae HP PGSS and +PT SS |
| 494          | P          | 2.77         | HSV-1 HSV-2 HPTPG C. neoformans HPT GSS and HP PGSS and HPTP SS and HP P SS C. pneumoniae HP PGSS and +PT SS |
| 495          | A          | 2.94         | HSV-1 HSV-2 HPTPG C. neoformans HPT GSS and HP PGSS and HPTP SS and HP P SS C. pneumoniae HP PGSS and +PT SS |
| 496          | P          | 2.89         | HSV-1 HSV-2 HPTPG C. neoformans HPT GSS and HP PGSS and HPTP SS and HP P SS C. pneumoniae HP PGSS and +PT SS |
| 497          | K          | 2.95         | HSV-1 HSV-2 HPTPG C. neoformans HPT GSS and HP PGSS and HPTP SS and HP P SS C. pneumoniae HP PGSS and +PT SS |
| 498          | T          | 2.98         | HSV-1 HSV-2 HPTPG C. neoformans HPT GSS and HP PGSS and HPTP SS and HP P SS C. pneumoniae HP PGSS and +PT SS |
| 499          | P          | 2.69         | HSV-1 HSV-2 HPTPG C. neoformans HPT GSS and HP PGSS and HPTP SS and HP P SS C. pneumoniae HP PGSS and +PT SS |
| 500          | P          | 2.51         | HSV-1 HSV-2 HPTPG C. neoformans HPT GSS and HP PGSS and HPTP SS and HP P SS C. pneumoniae HP PGSS and +PT SS |
| 501          | S          | 2.343        | HSV-1 HSV-2 HPTPG C. neoformans HPT GSS and HP PGSS and HPTP SS and HP P SS C. pneumoniae HP PGSS and +PT SS |
| 502          | S          | 2.123        | HSV-1 HSV-2 HPTPG C. neoformans HPT GSS and HP PGSS and HPTP SS and HP P SS C. pneumoniae HP PGSS and +PT SS |

a classical example from the field of population genetics and Darwinism, the light coloured genes of the peppered moth favour its selective predation by many different birds when it alights on dark trees covered with soot pollution, while darker melanised forms are selectively targeted on lighter coloured trees [273]. The coloration susceptibility genes, or the variety of tree (risk factors), do not kill the moth but allow several causes to do so. The causes can hide in plain sight, as epidemiological studies, as applied to human diseases, could conclude that the birds are not killing the moths, as they are always present, on both sets of trees, in both genetic conditions, whether the moths are alive or
Alzheimer's disease (C. neoformans and many other common pathogens). Many of the pathogens implicated in Alzheimer’s disease (herpes simplex, Borrelia burgdorferi and C. pneumoniae), and several other risk factors (cholesterol, homocysteine, diabetes, or vitamin A or nerve growth factor deficiency) are able to promote cerebral beta-amyloid deposition in animal models, without the aid of any gene variant. Subsets of susceptibility genes can be related to each of these amyloidogenic pathways [1]. In the case of genomewide association studies, the genes returned, as well as APP, beta amyloid, and gama secreta, seem intimately concerned with pathogen life cycles and defence and the immune network. This suggests that the diverse microbial risk factors as well as other dietary and environmental factors implicated in Alzheimer’s disease are in fact causative agents, whose deleterious effects are conditioned by susceptibility genes. As the environmental risk factors are amenable to therapy, while the susceptibility gene products have so far proved largely resistant, this suggests numerous ways with which to tackle the problem of Alzheimer’s disease.

Herpes Simplex Reactivation. Alzheimer’s disease plaques and tangles are highly enriched in human proteins used the herpes simplex during its life cycle, as well as in many immune-related proteins, suggesting that immune attack on a reactivated virus, diverted to neurones, which contain the complement membrane attack complex, may be ultimately responsible for the extensive neuronal destruction seen in Alzheimer’s disease [15]. The herpes simplex virus establishes latency in neurones, existing as a dormant form seen in Alzheimer’s disease [15]. The herpes simplex viral load is increased in APOE4 mice, while the viral load is much increased in APOE knockout mice, compared to APOE3 mice, suggesting that APOE4 favours the establishment of a greater number of latent viruses in cerebral tissue [274]. In neuroblastoma cells, this latent form may even exert beneficial effects, blocking apoptosis and promoting neurite extension via AKT1 upregulation [275]. However, this latent form can be reactivated by NGF deprivation [276], and NGF promotes viral latency via the TrkA receptor NTRK1 [277], the expression of which is reduced in the Alzheimer’s disease brain [278]. (Relevant pathways and genes: neurotrophin signalling (GSK3B, NTRK1, NTRK2, PIK3R1, and SOS2). Vitamin A supplementation in rats increases the cerebral levels of both NGF and BDNF [279], while oestrogen deficiency lowers cerebral NGF levels, an effect reversed by 17-beta oestradiol [280], which is, however, also able to reactivate the virus, via oestrogen receptor alpha (ERS1) [281]. High levels of total oestradiol have been reported as a risk factor for Alzheimer’s disease in both women and men [282, 283]. Vitamin A related gens include APOE4, the isoform least able to transport the vitamin A precursor retinyl palmitate, A2M ABCA1 ALB ALDH2 APOA1 CHD4 CLU CYP46A1 ESR1 GSTM1 GSTP1 HSPG2 KLF5 LIPA LPL LRAT LRP2 LRPAP1 MEF2A NPA2 NR1H2 PARP1 PIN1 POU2F1 PPARG RXRA THRA TTR UBQLN1 VDR and many others controlled by retinoid receptor element (reviewed in [126]).

The virus can also be reactivated by heat [284], IL6 [285], or TNF [286]. IL6 plasma and CSF levels have been reported to be increased in Alzheimer’s disease and the secretion of IL6 from monocytes is increased [287–289]. IL6 plasma levels are raised by infection with C. pneumoniae [290] or Helicobacter pylori [291], and IL6 production in monocytes is stimulated by C. neoformans [292]. Stress-activated corticosterone is also able to reactivate the virus [293] (pathway = steroid hormone biosynthesis: COMT, CYP19A1, HSD11B1). Cortisol levels are increased in the ageing population and in Alzheimer’s disease [294, 295]. A number of related stressors including adrenaline [296], or downstream effectors such as cyclic AMP, protein kinase A, or C activation [297] are also able to reactivte the virus. Herpes simplex reactivation is blocked by beta-receptor antagonism (ADRB1) [296, 298]. Glucocorticoids and prostaglandins are also able to reactivate the virus [299]: cyclooxygenase inhibitors (PTGS2), celecoxib and indomethacin block viral reactivation and nonsteroidal anti-inflammatory use has been associated with a lower incidence of Alzheimer’s disease. Lysophosphatidic acid is also able to reactivte the virus [300] (LPAR5). Hypoxia also increases the replication of herpes simplex [301]: transient cerebral ischaemia also lowers NGF levels [302], and these effects are relevant to the cerebral hypoperfusion seen in ageing and in Alzheimer’s disease [303]. Vitamin A and the retinoic acid isomers all-trans-, 9-cis-, and 13-cis-Retinoic Acid are all able to reduce viral replication [304]. Low Vitamin A levels are a problem in the ageing population and even in successfully ageing persons can be observed in 50% of the population over the age of 80–85 [305]. Low vitamin A levels are also a risk factor for Alzheimer’s disease [306]. Mice deficient in the nitric oxide synthase NOS2 are also more susceptible to herpes virus infection, and reactivation occurs is stimulated by caspase 3 activation (CASP3) [135].

Thus, fever or cytokine release induced by diverse infections might be expected to reactivate herpes simplex as would several of the conditions associated with Alzheimer’s disease (cerebral hypoperfusion, low cerebral NGF levels, vitamin A deficiency, or high oestradial levels).

3.6.6. The Microbiome in Alzheimer’s Disease. These pathogens form a very small proportion of an extensive human microbiome comprising of trillions of bacteria, viruses, and other pathogens, whose influence on diseases is increasingly recognised [307]. Individual species may exert benevolent or malevolent effects which may well be dictated by the very extensive sequence homology between human and pathogen proteins which enables pathogens to intercalate with numerous important signalling networks, via competition with their human counterparts [239, 241, 248, 250, 254]. These networks are implicated in diseases, and their efficiency, as well as pathogen/host homology, is dictated by susceptibility genes. This host/pathogen matching covers
the entire human proteome and is represented by millions of short consensi of pentapeptides or more, not counting the longer gapped consensi. Clearly, powerful algorithms are needed to trawl human and pathogen proteomes and to link these homologies to susceptibility genes and to epitopes and autoantigens.

The principles discussed here may apply to many other, if not most, human diseases.

Protective Agents in Alzheimer’s Disease. Statins [308], fish consumption [309], omega-3 polyunsaturated fatty acids [310], the Mediterranean diet [311], nonsteroidal anti-inflammatories [312], or the generally healthy life-style of nuns living in convents [313] have all been associated with a reduced incidence or severity of Alzheimer’s disease, while homocysteine lowering B vitamins and folate have been shown to slow the rate of brain atrophy in cognitively impaired elderly patients [314]. A rather pessimistic study [315] recently stated that no firm conclusions could be drawn on the association of any modifiable factors with risk of Alzheimer’s disease. While this may be a justifiable statistical conclusion from meta-analysis, this is not to reckon with the diversity of the underlying genomic platform of each individual or with the profusion of diverse interacting risk and protective factors (epistasis, gene/environment, and environment/environment interactions).

As with the risk factors, protective agents can be linked to genetic and pathological pathways involved in cholesterol and lipid function (statins, fish, and diet, e.g., ABCA1, ABCA2, ABCA7, ABCG1, ACADS, ALDH2, APP, APOA1, APOA4, APOA5, APOC1-4, APOE, CH25H, CYP46A1, DHCR24, FDP5, HMGCGR, HMGC52, HSD11B1, LIPC, LP1, LP2, LP8, LDLR, LIPA, LPL, OLRI, PPARA, PPARG, PTPLA, VLDLR, NPC1, NPC2, SOAT1, SREBF1), homocysteine, methionine, and folate metabolism (folate and vitamins, e.g., BLMH, CBS, COMT, NAT2, MTHFD1L, MTHFR, MTR, MTRR, PON1, PON2, PON3, VDR) and inflammatory pathways (NSAID’s e.g., C4A, C4B, CDP2AP, CD33, CFH, CCL2, CCL3, CCR2, CSF1, CLU, CR1, FAS, GSK3B, IL1A, IL1B, IL6, IL8, IL10, IL18, PLA2, SERPINA1, SERPINE1, SERPINF2, PTGS2, TGFBI, TNF). As with the risk factors, the success of such protective agents is likely to be determined by genes and other confounding factors. In this genomic era, affordable whole genome sequencing will soon be achieved, ushering in an age of more effective treatments tailored to individual genetic profiles. Alzheimer’s disease is clearly multifactorial with many related genetic and environmental risk factors, several underlying pathologies, and several available protective strategies. A recent study has also shown that many other seemingly benign factors (eyelash, hearing, denture wearing, stomach, kidney, bladder or bowel problems, coughs, and colds) as well as high blood pressure and diabetes, constituting a frailty index, combine to markedly increase both the incidence and severity of Alzheimer’s disease [316]. A further study, identifying physical inactivity, depression, smoking, mid-life hypertension or obesity, low education, and diabetes as key risk factors, has estimated that ∼50% of Alzheimer’s disease cases may be preventable [317].

Elimination of the risk factors, including the regular detection and elimination of pathogens in the elderly, adherence to sensible dietary and vitamin supplement recommendations, and the genetically tailored use of certain drug regimens are together likely to be able to markedly reduce the incidence of Alzheimer’s disease. Using phage display, it is now possible to express peptide fragments of the entire human proteome in a phage library, and to use this to trap autoantibodies in blood or other bodily fluid samples. The antigen expressed by the labelled phage can be identified by high throughput sequencing [318]. Such technology is likely to be extremely useful in characterising biomarkers and pathological immune processes as well as potential pathogen/human cross-reactivity.

Proteome-wide characterisation of the autoantibodies relevant to Alzheimer’s disease (a move from GWAS to PWAS) would also be very informative as selective autoantibody removal via affinity dialysis might well be expected to influence the severity and progression of Alzheimer’s disease.

Since the submission of this paper, Miklossy has reported a highly significant association between spirochete infection and Alzheimer’s disease. As well as B. burgdorferi, several periodontal pathogen treponemases species were detected in brain samples and the pathological features of Alzheimer’s disease were reproduced by infection in vitro [319]. In addition, two groups have reported a very extensive repertoire of autoantigens in Alzheimer’s disease, which can be characterised with a high degree of accuracy by a definitive immunosignature [320, 321]. The principles outlined above could thus be tested by analysis of pathogen/autoantigen cross-reactivity.

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