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Research Article

Alzheimer's Disease: A Pathogenetic Autoimmune Disorder Caused by Herpes Simplex in a Gene-Dependent Manner

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Herpes simplex is implicated in Alzheimer's disease and viral infection produces Alzheimer's disease like pathology in mice. The virus expresses proteins containing short contiguous amino acid stretches (5–9aa "vatches" = viralmatches) homologous to APOE4, clusterin, PICALM, and complement receptor 1, and to over 100 other gene products relevant to Alzheimer's disease, which are also homologous to proteins expressed by other pathogens implicated in Alzheimer's disease. Such homology, reiterated at the DNA level, suggests that gene association studies have been tracking infection, as well as identifying key genes, demonstrating a role for pathogens as causative agents. Vatches may interfere with the function of their human counterparts, acting as dummy ligands, decoy receptors, or via interactome interference. They are often immunogenic, and antibodies generated in response to infection may target their human counterparts, producing protein knockdown, or generating autoimmune responses that may kill the neurones in which the human homologue resides, a scenario supported by immune activation in Alzheimer's disease. These data may classify Alzheimer's disease as an autoimmune disorder created by pathogen mimicry of key Alzheimer's disease-related proteins. It may well be prevented by vaccination and regular pathogen detection and elimination, and perhaps stemmed by immunosuppression or antibody adsorption-related therapies.

1. Introduction

Herpes simplex infection (HSV-1) has been shown to be a risk factor in Alzheimer's disease; acting in synergy with possession of the APOE4 allele HSV-1 infection in mice or neuroblastoma cells increases beta-amyloid deposition and phosphorylation of the microtubule protein *tau* [1–5]. Viral infection in mice also results in hippocampal and entorhinal cortex neuronal degeneration, brain shrinkage, and memory loss, all as found in Alzheimer's disease [6]. A recent study has also shown that anti-HSV-1 immunoglobulin M seropositivity, a marker of primary viral infection or reactivation, in a cohort of healthy patients, was significantly associated with the subsequent development of Alzheimer's disease. Anti-HSV-1 IgG, a marker of lifelong infection, showed no association with subsequent Alzheimer's disease development [7]. All of these factors support a viral influence on the development of Alzheimer's disease. As shown below, proteins expressed by HSV-1 are homologous to all of the protein products of the major susceptibility gene in Alzheimer's disease (APOE, clusterin, complement receptor 1, and PICALM) as well as to APP and *tau* and over 100 others implicated in genetic association studies. This suggests that Alzheimer's disease is a "pathogenetic" disorder caused by HSV-1 (and other infections) that mimic these key susceptibility targets.

2. Methods

The Human herpesvirus 1 genome (NC_001798) was screened against the human proteome using the NCBI BLAST server with and without the Entrez Query filters ("Alzheimer" or "cholesterol") [8]. Each BLAST re-turns a large list of human proteins, many of which display homology to several different HSV-1 proteins. A Tag cloud generator was used to quantify these different interactions http://www.tagcloud-generator.com/index.php. This generates tags whose font size is proportional to the number of viral protein hits per human protein. The tag size scale was set from 1 to 20. Antigenicity (B cell epitope

Table 1: The antigenicity index (B cell epitope) for single amino acids defined by the BepiPred server. The top 6 scoring amino acids are highlighted in grey in the various tables.

Symbol	Amino acid	B-epitope antigenicity
P	Proline	0.145
G	Glycine	0.035
D	Aspartate	0.018
E	Glutamate	0.003
S	Serine	−0.008
T	Threonine	−0.011
Q	Glutamine	−0.012
N	Asparagine	−0.013
A	Alanine	−0.024
W	Tryptophan	−0.025
K	Lysine	−0.031
R	Arginine	−0.062
H	Histidine	−0.071
V	Valine	−0.112
F	Phenylalanine	−0.138
I	Isoleucine	−0.138
M	Methionine	−0.138
C	Cysteine	−0.175

prediction) was predicted using the BepiPred server [9] at http://www.cbs.dtu.dk/services/BepiPred/ and T cell epitopes predicted using the Immune epitope database resource at http://tools.immuneepitope.org/main/html/tcell_tools.html [10]. The immunogenicity index for individual amino acids is shown in Table 1. References for genetic association studies can be found at http://www.polygenicpathways.co.uk/alzpolys.htm. References for herpes simplex host viral interactions can be found in a database at http://www.polygenicpathways.co.uk/herpeshost.html. Protein kinases phosphorylating the microtubule protein *tau* were identified from the Kinasource database at http://www.kinasource.co.uk/Database/welcomePage.php and from the material available at the ENTREZ gene interaction section for *tau* (MAPT).

Because of the large volume of data generated by the BLASTs, raw BLAST data have been made available at http://www.polygenicpathways.co.uk/Alzheimer.htm. This survey is restricted to the herpes simplex virus, HSV-1, but similar data were obtained for other viral or pathogen species implicated in Alzheimer's disease, where similar conclusions apply. These BLAST files and a summary of the results are available on the PolygenicPathways website at http://www.polygenicpathways.co.uk/BLASTS.htm.

3. Results

The results of the HSV-1 BLASTS, sized according to the number of viral hits per protein, using the filter "Alzheimer," are shown in Table 2. Over a hundred human gene products, including all of the major Alzheimer's disease susceptibility gene products (APOE4, clusterin, complement receptor 1, and PICALM) and most of many other diverse genes that have been implicated in Alzheimer's disease in genetic association studies contain intraprotein sequences that are identical to those within herpes simplex viral proteins. The alignment with complement receptor 1 (CR1) has functional consequences, as glycoprotein C of the virus acts as a CR1 mimic, binding to other complement components (C3 and its derivatives) blocking the complement cascades and preventing formation of the membrane attack complex [12, 13]. This nicely illustrates one of the functional consequences of this type of mimicry.

The type of viral homology for various different protein classes is shown in Table 3. These classes include products involved in APP signalling and processing (BACE1 and 2 and gamma-secretase components), cholesterol and lipoprotein function, *tau* function, inflammation, and oxidative stress, all of which are key processes disrupted in the Alzheimer's disease brain.

Using the filter "cholesterol," a number of cholesterol and lipoprotein-related proteins again contain numerous sequences corresponding to those found in herpes viral proteins. This group of proteins play an important role in Alzheimer's disease pathophysiology [14–17].

The unfiltered BLAST returns the human proteins with the greatest homology to viral proteins and showed that herpes simplex viral proteins are highly homologous to a series of family members of diverse protein kinases. Several of these are known to phosphorylate the microtubule protein *tau*, an effect that is observed following HSV-1 infection [5]. The homology is such as to suggest that such phosphorylation may be accomplished by the viral proteins themselves, as well as by human protein kinases (Table 4).

This type of mimicry is by no means restricted to the herpes simplex virus as APOE4, clusterin, complement receptor 1, and PICALM are homologous to proteins from a diverse array of phages and viruses including phages that affect commensal bacteria, the influenza virus, and the HHV-6 virus which has a seroprevalence approaching 100% [18] (Table 5). Because of the universality of the phenomenon of viral matches within the human proteome, most proteins will be homologous to proteins from specific subsets of viruses. Viruses and other pathogens expressing proteins with homology to key susceptibility gene products might however be considered as important potential environmental risk factors. For the major Alzheimer's disease gene candidates, several herpes species other than HSV-1 (HSV-2, 3, 6, 6B, and 8) fall into this category (Table 5).

The tables in supplementary data on the website http://www.polygenicpathways.co.uk/alzheimer.htm show that numerous Alzheimer's disease susceptibility gene products are also homologous to proteins expressed by other pathogen risk factors in Alzheimer's disease, including Chlamydia pneumonia, which has recently been detected in the Alzheimer's disease brain [19].

Cryptococcus neoformans, Helicobacter pylori, Porphyromonas gingivalis (one cause of the gum disease that is a risk factor in Alzheimer's disease [20]), Borrelia Burgdorferi,

Table 2: Human proteins with homology to HSV-1 proteins: The size of symbol (HUGO Nomenclature approved gene symbols) is proportional to the number of viral proteins displaying homology to the gene product. Filter "Alzheimer": all of the genes encoding for these proteins with the exception of those with the strikethrough have been implicated in Alzheimer's disease in genetic association studies. Filter "cholesterol": genes encoding for proteins products in dashed boxes have been implicated in Alzheimer's disease in genetic association studies. No Filter: HSV-1 proteins are most homologous to diverse families of kinases: Those boxed have been shown to phosphorylate the microtubule protein *tau* (Data from Kinasource and from NCBI Interactions section for the MAPT gene (*tau*)).

BLAST filter	Gene products with homology to HSV-1 proteins
HSV-1 Filter "Alzheimer"	**Major genes** APOE4 CLU CR1 ~~CR1L~~ **APP related** APLP1 APP ~~APBA1~~ ~~APPBA2~~ APBB1 APBB2 APBB3 COL25A1 MAPK8IP1 IDE SERPINA3 SNCA ~~PBLD~~ **Secretase related** BACE1 BACE2 NCSTN PEN2 PSEN1 PSEN2 **tau related** MAPT GSK3B **Lipoprotein/cholesterol related** A2M CH25H HMGCR LRP1 OLR1 SORCS1 SORCS3 SORL1 Channels CACNB2 OXIDATIVE STRESS ATP6 COX2 ~~COX3~~ CYTB HMOX1 ~~NADH4L~~ ND1 ND4 NQO1 Cytokine/immune ~~CX3CL1~~ MICB MISCELLANEOUS ALDH18A1 ~~ATP2C1~~ BLMH PRNP CALHM1 ~~CBARA1~~ ~~CELF5~~ CTNNA3 DLD DKK1 DLST DNTT DPYSL2 ECE1 ~~ENTPD2~~ FAM3A GAPDH DHCR24 ~~FKBP1A~~ GDI2 GOLM1 ~~HERC4~~ IFIT5 ~~ITMA2~~ ITM2B ~~KIN~~ TFCP2 CHAT LHPP LRRTM3 MAPK10 ~~NOTCH4~~ ~~SAMD8~~ SLC6A4 ~~SLC17A5~~ ~~SERPINI1~~ ~~SHISA4~~ ~~PDLIM2L~~ ~~PHYH~~ PLAU PTPLA SMPD1 S100B ~~TAPBP~~ TET1 UBQLN1 ND5 BTBD16 IL1A ATP8 CALHM2 CTSD RELN COPS8 PZP UCHL1 ZNF224 ZNF225
Hsv-1 Query Cholesterol	**ATP cassette** ABCA3 ABCA6 ABCA9 ABCA10 ABCD2 ABCG8 **Apolipoprotein** APOB APOC1 APOE APOL3 APOM **CYP450** CYP2A7 CYP2C19 CYP4A11 CYP4F2 CYP11B2 CYP24A1 CYP2U1 **Lipoprotein receptors** LDLR LDLRAD2 LDLRAD2 PLA2G15 LRP1 LRP2 LRP3 LRP4 LRP6 LRP9 LRP10 LRP11 LRP12 VLDLR Cholesterol metabolism/transport CES2 CHST6 DHCR2 DHCR7 EBP HMGCR HMGCS2 LSS MSR1 NPC1 NPC2 OSBP OSBPL2 SCP2 SORBS1 TSPO Cholesterol/lipoprotein transcription factor SREBF1 SREBF2 **MISCELLANEOUS** ACSM1 ACAA2 ACAD8 ALOXE3 ALOX5 ALOX12B ALOX15B AMOT ATMIN ATP2B2 ATP2C1 ARHGAP33 BUD13 CAL CD320 CDKN1C CEBPD CELSR2 CFDP1 CFI CHRM1 CHST5 C8B CLEC3A CRHR1 CUBN DGAT1 DISC1 DPP7 FXDR GABRA2 GHRH GULP1 IL28A INSR IRS4 KCNV2 KDR KL KLB KLRAQ1 ABCA2 MALL MAMDC4 MED15 MED23 MBTPS1 MSS NCOA6 NDN PKM2 PRKAG3 PROM2 WIPI1 MBTPS2 PRKAA2 CYP21A2 TRIB1 SORL1 PRKAG2 PTGIS RAB7L1 RAB8A S4 SBF2 SCAND1 SLC6A9 SLC27A1 ST14 SULT2B1 PIK3C2G ABCA5 TBXAS1 TFCP2L1 TMPRS TOMM40 PSCR1 PTPN1 WDR59 ABCA4 E2F4 RXFP1 BCAR1 PRKAA1 PRKAG1 CYP27C1 PCSK9 GLG1 SLC12A4 NUP93

Table 2: Continued.

BLAST filter	Gene products with homology to HSV-1 proteins
HSV-1 No Filter	**KINASES** ARAF BRAF CAMK1D CAMK1G CAMK2B CAMK2D CAMK2G CDK1 CDK4 CDK10 CDK2 CDK3 CDK6 CDK7 CDK8 CDK9 CDK12 CDK13 CDK16 CDKL1 CDKL2 CDKL4 CDKL5 CHEK2 CHUK DCLK2 DMPK EIF2AK3 EIF2AK4 GSK3A GSK3B HUNK ICK IKBKB MAK MAPK1 MAPK3 MAPK4 MAPK6 MAPK8 MAPK12 MAPK14 MAP2K2 MAP3K2 MAP3K3 MAP3K4 MAP3K12 MAP3K13 MAP4K1 MARK2 MARK3 MARK4 MYLK NEK3 NEK9 NEK11 NUAK1 NUAK2 PAK1 PAK3 PAK6 PASK PCNK PHKG2 PLK2 PLK3 PRKAA1 PRKAA2 PSKH1 RPS6KA1 RPS6KA2 RPS6KA3 RPS6KA6 SBK2 SGK1 SGK494 SIK1 SLK SNRK STK10 STK24 STK25 STK35 STK39 TAOK1 TAOK2 TSSK2 **MISCELLANEOUS** ADAMTS17 APOA1BP APBB1 CEP250 C4A COL25A1 DNM3 EIF3F EIF3FP3 FADD LAMA3 LATS1 LOR MASTL MST4 NIM1 NTN1 OXSR1 PICALM POLA1 POLD1 SGK2 RAGE REV3L RRM2B STARD9 TMEM175 EIF2AK2 MAPK9 TSC22D4 TSC2 H1FNT SRRM1 MAPK11 CDKL3 RRM1 RAF1 SIK2 RASAL3 APP BTBD3 DYRK1B complement component 4B Complement receptor type 1 MELK MAPK13 PNCK MAP2K1 PAK4

[21], Human herpesvirus 6, and Human herpesvirus 5 (Cytomegalovirus) [22].

Cryptococcus neoformans infection has been shown to be associated with a rare but curable form of dementia in two separate studies, where both patients had been consigned to healthcare for 3 years, with a diagnosis of Alzheimer's disease. Both recovered normal function following antifungal treatment [23, 24]. Heliocobacter pylori eradication has also been reported to improve cognitive function in Alzheimer's disease [25].

The protein sequences highlighted in grey in Table 3 contain strings of herpes simplex proteins that have been shown to bind to several interactome partners of *tau* [11] (see http://www.polygenicpathways.co.uk/herpeshost.htm) and are those most likely to form epitopes that cross-react with their human counterparts (Table 1). These include APOE4, complement receptor 1, clusterin, insulin degrading enzyme, the APP homologue, APLP2, the APP binding protein APBBI1P, the collagen amyloid plaque component CLAC, synuclein, and the foetal Alzheimer antigen, ALZ50. Tau appears to be highly antigenic (Table 2).

This antigenicity was further studied for the two key proteins in Alzheimer's disease, beta-amyloid and *tau*, and the predicted immune epitopes compared with the HSV-1 viral proteins aligning within these various regions (Figures 2 and 3).

4. Vatches within Beta-Amyloid and the Microtubule Protein *tau*

Vatches (= viralmatches) are short contiguous amino acid stretches that are identical in viral and human proteins [26, 27]. There are several million within the human proteome, derived from evolutionary descent and from the insertion of multiple viruses into the human genome over millions of years. This type of insertion is not restricted to retroviruses, as herpes viruses, hepatitis viruses, influenza and the common cold virus, the coronavirus, and the papillomavirus, among others, have all been inserted into different genomic regions or are homologous to the encoded protein products. This has occurred on several occasions during evolutionary time, and these reinsertions appear to be responsible for the creation of gene families (see http://www.polygenicpathways.co.uk/blasts.htm), where over 2 million such alignments are available for multiple viral species. In effect, the entire human genome appears to be composed of viral DNA. For example, the coverage of human chromosome 10 is complete, with 119,867 human/viral DNA matches.

A single HSV-1 vatch, translated back to DNA, is identical to DNA in 103 different genomic regions covering several human chromosomes. This phenomenon is likely responsible for the creation of gene families, and the HSV-1

Table 3: Major susceptibility gene products and members of other key signalling networks in Alzheimer's disease (Sbjct) aligning with the translated HSV-1 genome (Query). The 6 amino acids with the highest B cell antigenicity index are highlighted in grey (see Table 1). Spaces denote a nonidentical amino acid; dashes represent gaps and + = conserved amino acid (similar physicochemical properties).

Human protein	Alignment with the HSV-1 translated genome		
APOE4 1B68A GI:15826311	Query 139585	VRG RLV **VRG RLV**	139568
	Sbjct 111	VRG RLV	116
PICALM NP_009097.2 phosphatidylinositol binding clathrin assembly protein	Query 35856	P ATTP T **P ATTP T**	35873
	Sbjct 601	P ATTP T	606
Complement receptor 1 complement receptor type 1 isoform S precursor NP_000642.3	Query 39696	SSPPPR SSPPPR	39679
	Sbjct 2029	SSPPPR	2034
Clusterin isoform 1 NP_001822	Query 48155	SPGGAR **SPGGAR**	48138
	Sbjct 30	SPGGAR	35
APP processing and related			
3DXCA chain A, crystal structure of the intracellular domain of human APP in complex with Fe65	Query 78347	TE AVLG **TE AVLG**	78364
	Sbjct 64	TE AVLG	69
EAX09965.1 amyloid beta (A4) precursor protein (peptidase nexin-II, Alzheimer)	Query 102020	RD P S E LRNTAAS G PD **RDP L TAAS PD**	102064
	Sbjct 359	RDP VKLP TTAAS TP D	373
NP_958816.1 amyloid beta A4 protein isoform b precursor	Query 75494	AEEIAD QV-E ILVD QTE **AEEI D+ VE L Q E**	75447
	Sbjct 536	AEEIQD E VD E LL--QKE	550
NP_620428.1 beta-secretase 1 isoform B preproprotein	Query 96347	WS LLWLG AG V **W LLW+GAGV**	96376
	Sbjct 7	WLLLWMG AG V	16
NP_620477.1 beta-secretase 2 isoform B preproprotein BACE2	Query 148387	ARATL-P VMKE LLLRAAP E **ARA L P LLRAAPE**	148334
	Sbjct 5	ARALLLP LLAQWLLRAAP E	23
AAM92013.1beta-site APP-cleaving enzyme BACE1	Query 59005	IFD RTRKFVLACP RAG F **+FDR RK R GF**	58955
	Sbjct 59	VFD RARK- - - - - - RIG F	69
	Query 115596	AVS ACQV **AVSAC+V**	115576
	Sbjct 70	AVS ACHV	76
EAW81096.1 presenilin 1 (Alzheimer disease 3), isoform CRA_f	Query 134424	FLP E WTVAW **+LPE WT AW**	134398
	Sbjct 240	YLP E WT- AW	247
EAW69799.1 presenilin 2 (Alzheimer disease 4), isoform CRA_d	Query 40896	ALP P LP IS **ALP LPIS**	40873
	Sbjct 152	ALP ALP IS	159

Table 3: Continued.

Human protein	Alignment with the HSV-1 translated genome		
NP_758844.1 gamma-secretase subunit PEN-2	Query 151699	G YVWRS	151716
		G YVWRS	
	Sbjct 55	G YVWRS	60
	Query 142209	S AVG G LFW	142186
		S AVG LFW	
	Sbjct 60	S AVG FLFW	67
NP_004960.2 insulin-degrading enzyme isoform 1 precursor	Query 25849	P E D RRE YP G	25875
		PED RE Y G	
	Sbjct 58	P ED KREYRG	66
NP_061916.3 amyloid beta A4 precursor protein-binding family B member interacting protein APBB1IP	Query 26756	D NHLP S P AP P TP -D D IS CG P E LP FAR PP	26673
		D+ LP P PP P DD PELP PP	
	Sbjct 551	D D FLPPP P P P P P LD D ---- P E LP ---- P P	571
NP_004877.1 amyloid beta A4 precursor protein-binding family A member 3 [Homo]	Query 148163	LE P AS RLLRLG RP P E	148119
		LEP A RLL PPE	
	Sbjct 132	LE P AP RLL - - - QP P E	143
NP_001633.1 amyloid-like protein 2 isoform 1 APLP2	Query 73214	IS MTP VAVLWE NP D P P G P P D VRFVG SE ATE E LP	73116
		IS TP V DVR V SE EE P	
	Sbjct 579	IS E TP V- - - - - - - - - - - - D VR - VS S E E S E E IP	597
	Query 63557	E VVE -RTD VYYYE T	63595
		EVVE R - D YYY+T	
	Sbjct 266	E VVE D R-D -YYYD T	277
NP_001123886.1 amyloid beta A4 precursor protein-binding family A member 2 isoform	Query 20300	LRRG D G D L	20323
		LRRGDGDL	
	Sbjct 212	LRRG D G D L	219
AAL79526.1AF394214_1 adaptor protein FE65a2	Query 63303	S S TRG LWTP SH	63335
		S S R WTP SH	
	Sbjct 572	SSS RE QWTP S H	582
NP_663722.1 amyloid beta A4 precursor protein-binding family B member 1 isoform	Query 51630	RG LRG P VLI	51604
		RGLRGP LI	
	Sbjct 130	RG LRG P G LI	138
Query Q12830.3BPTF_Fetal Alzheimer antigen Alz-50 clon	Query 41203	P AP P P FRS ARNTCP LP P S P TAS G P	
		PAPPP PP P S GP	
	Sbjct 22	P AP P P- - - - - - - - - P P P P P TS G P	
Query O94985.1 CSTN1 Calsyntenin-1 = Alcadein	Query 43114	AS RLLL	43131
		A RLLL	
	Sbjct 12	AARLLL	17
NP_009292.1 alpha-synuclein isoform NACP112	Query 54520	E D AVHG VAG V	54549
		E VHGVA V	
	Sbjct 46	E G VVHG VATV	55
Others			
Query Q07954.1LRP1_HUMAN RecName: Full=Prolow-density lipoprotein receptor-related protein	Query 92727	TIHRE TGSG	92701
		T+HRETGSG	
	Sbjct 1425	TVHRE TGSG	1433

Table 3: Continued.

Human protein	Alignment with the HSV-1 translated genome		
NP_000577.2 interleukin-2 precursor	Query 27667	S AP TS S S **SAPTSSS**	27647
	Sbjct 20	S AP TS S S	26
NP_002084.2 glycogen synthase kinase-3 beta isoform 1	Query 86718	G RP RTTS **GRPRTTS**	86698
	Sbjct 3	G RPRTTS	9
NP_065574.3 choline O-acetyltransferase isoform 2 [Homo sap]	Query 67995	AQS AE PRRA----CVP **A+ AEPRRA C+P**	68030
	Sbjct 87	AE AAE PRRAG P HLCIP	102
NP_003947.1 cholesterol 25-hydroxylase	Query 66447	WVPALRR **WVPALRR**	66467
	Sbjct 64	WVPALRR	70

Table 4: Alignment of the HSV-1 translated genome (Query) with 3 protein kinases known to phosphorylate *tau* (Sbjct). Glycogen synthase kinase GSK3A aligns with the same amino acids as GSK3B. CAMK2B: calcium/calmodulin-dependent protein kinase II beta. MAPK1: mitogen-activated protein kinase 1 (erk2).

Kinase	Alignment with HSV-1 proteins		
GSK3B and GSK3A	Query 136083	QLLSAVDYIHRQGIIHRDIKTENIFINTPE----DICLGDFGAA----------CFV **QL YIH GI HRDIK +N + P+ C DFG A C**	
	Sbjct 143	QLFRSLAYIHSFGICHRDIKPQNLLLD-PDTAVLKLC—DFGSAKQ LVRG EPNVSYIC--	
	Query 136212	QGSRSSPFPYGIAGTIDTNAPEVL--AGDPYTTTVDIWSAG **SR Y APE A D YT +D+WSAG**	136328
	Sbjct 198	--SR-----Y-------YRAPELIFGATD-YTSSIDVWSAG	223
	Query 81948	HPW----RSRTAPGAAALC **HPW R RT P A ALC**	81992
	Sbjct 278	HPWTKVFRPRTPPEAIALC	296
CAMK2B	Query 136083	QLLSAVDYIH-RQ-GIIHRDIKTENIFINTPEDI-----C------LGDFGAACFVQG VQG -- **Q L AV H Q G++HRDK PE+ C L DFG A VQG**	136217
	Sbjct 119	QILXAV--LHCHQMGVVHRDLK--------	
	Query 136218	-SRSSPFPYGIAGTIDTNAPEVLAGDPYTTTVDIWSAGLVI **+G AGT PEVL + Y VDIW G VI**	136337
	Sbjct 169	QAW-----FGFAGTPGYLSPEVLRKEAYGKPVDIWACG-VI	203
MAPK1	Query 136083	QLLSAVDYIHRQGIIHRDIKTENIFINTPEDIC----LGDFGAACFVQGSRSSPFPYGI **QLL YIH GIIHRD K N+ +N ED C L DFG A R**	
	Sbjct 133	QLLRGLKYIHSAGIIHRDLKPSNVAVN--ED-CELRIL-DFGLA------RQ-------A	175
	Query 136251	-----GTIDT---NAPEVL-----AGDPYTTTVDIWSAG **G + T APE++ Y TVDIWS G**	136328
	Sbjct 176	DEEMTGYVATRWYRAPEIMLNWMH----YNQTVDIWSVG	210

virus appears to have been partly responsible for the creation of lipoprotein receptor families (Figure 1), and of numerous kinases within a number of different families (see above and Table 2). Over millions of years, these DNA inserts have been extensively shuffled by recombination, but millions of consecutive sequences are retained that encode for the viral matching protein components.

Some of the vatches within beta-amyloid and *tau* are illustrated in Figures 2 and 3 which also demonstrates the B cell and T cell antigenicity of these proteins. As can be seen, there are numerous HSV-1 vatches within both proteins, many of which correspond to highly antigenic regions of APP or *tau*, and therefore also of the HSV-1 proteins.

In addition to the herpes simplex virus, a large number of other viruses express proteins containing a VGGVV sequence that is identical to that of a C-terminus peptide within beta-amyloid. Although not the most immunogenic

Table 5: Other viruses expressing homologous proteins for the four major Alzheimer's disease susceptibility gene products.

Alzheimer's gene	Viral protein	Identical amino acid sequences (vatches)
APOE4 Chain A, Apolipoprotein E4 (Apoe4), 22k Fragment. ACCESSION 1B68_A	ACE82482 polyprotein Hepatitis C virus subtype 1a	**GADMEDV**
	YP_002455799 tape measure protein Lactobacillus phage Lv-1	**MKELKA**
	ADD95207 hypothetical protein uncultured phage MedDCM-OCT-S04-C650	**RKRLLR+ ++L K L**
	YP_002242088 gp31 Mycobacterium phage Konstantine	**RKR-----D+LQ-RL----A-G-REGAE-GLS**
	YP_002922735 gp63 Burkholderia phage BcepIL02	**E EP P Q WQSGQ**
	NP_612835 major capsid protein Clostridium phage phi3626	**E EP-P----Q--WQSGQ**
	AAT07716 virion protein human herpesvirus 3	**LEEQLT--A**
	DAA06495 envelope glycoprotein 24 human herpesvirus 5	**DDL--R-LAVYQA**
	YP_001293401 hypothetical protein PPF10_gp057 Pseudomonas phage F10	**MTR---EFLKVA-Q**
Clusterin isoform 1 NP_001822.2	ACS93434 capsid portal protein human herpesvirus 5	**QVAERL**
	CAA35329 HCMVUL127 human herpesvirus 5	**SAINT**
	T44166 hypothetical protein U20 imported—human herpesvirus 6 (strain Z29)	**L +QTVSD+** and
	AF157706_21 U20 human herpesvirus 6B	**L LEE K D**
	P60504ICP47_HSV2S ICP47 protein;	**A LRRELD**
	NP_044506 large tegument protein human herpesvirus 2	**ESGQ LG**
	AAR12147 US34 human herpesvirus 5	**GSGLV R+L +F**
	AAA66443 unknown protein human herpesvirus 2	**+SGQVLG□-T**
	D1LR45_9INFA D1LR45 Hemagglutinin Influenza A virus	**LIEKTN++**
Clusterin isoform 2 NP_976084.1	ACS93434 capsid portal protein human herpesvirus 5	**QVAERL**
	C3U7E2Influenza A virus	**KYVNKE** and **LIEKTN E**
	C3VE93 Envelope glycoprotein (Fragment) human immunodeficiency virus	**KKKKEDAL**
	D2XAW9 Restriction endonuclease Marseillevirus	**EECKPC K**
	Q5J5Q8 Gp46 Mycobacterium phage	**DDDRTVC**
	Q9DVL9_9HIV1 Q9DVL9 Envelope glycoprotein gp160 human immunodeficiency virus	**NETRE**
	ORF10 Vibrio phage	**EKALQEY L RKY ELLK**
	Q2PZB7 RstR-like protein Vibrio phage CTX	**LLEQLNE+**
	P36272 Portal protein Enterobacteria phage P21	**TEFIREG**
Clusterin isoform 3 NP_001164609.1	ACS93434 capsid portal protein human herpesvirus 5	**QVAERL** and **RV GSGLV R+L +F**
	NP_050200 glycoprotein human herpesvirus 6	**L +QTVSD+**
	NP_050228 glycoprotein O human herpesvirus 6	**DESLQ A**
	YP_001129444 BFLF1 human herpesvirus 4 type 2	**SGVTEV**
	NP_044506 large tegument protein human herpesvirus 2	**ESGQ LG**
	AAA66443 unknown protein human herpesvirus 2	**+SGQVLG T**
	D1LR45 Hemagglutinin Influenza A virus	**LIEKTN++**
CR1 isoform f NP_000564.2	ACL67924 single-stranded DNA-binding protein human herpesvirus 3	**F SCEPS D**
	P88903_HHV8 P88903 ORF 4 human herpesvirus 8 type M PE = 4 SV = 1	**WDPPL KC**
	AAD49671AF157706_89 U79 human herpesvirus 6B	**SVPVCE**
	ABI63477 UL15 human herpesvirus 1 CAB06775 UL15 human herpesvirus 2	**Y+LRGAA**
	ACN63150 pUL27 human herpesvirus 5	**VRAG C TPE +RCRRK**
	ACS92020 tegument protein UL14 human herpesvirus 5	**L+GS SATC**
	NP_042926 protein UL49 human herpesvirus 6 BAA78254 capsid protein human herpesvirus 6B	**HCVL-GMK**
	ABI63477 UL15 human herpesvirus 1 NP_044484 DNA packaging terminase subunit 1 human herpesvirus 2	**Y+LRGAA**

Table 5: Continued.

Alzheimer's gene	Viral protein	Identical amino acid sequences (vatches)
	CAA35376 HCMVUL61 human herpesvirus 5	GPPAP LP
	:Q01016-2 Q01016 Isoform 2 of Complement control protein homolog Saimiriine herpesvirus 2	WDPPL-KC
	:Q01016-2 Q01016 Isoform 2 of Complement control protein homolog Saimiriine herpesvirus 2 (strain 11)	GSVVTY CN G
CR1 isoform S NP_000642.3	Q2HRD4 ORF4 human herpesvirus 8 type P (isolate GK18)	WDPPL KC
	ACL51139 helicase-primase primase subunit human herpesvirus 5 NP_050259 DNA replication human herpesvirus 6 AAD49671AF157706_89 U79 human herpesvirus 6B	SVPVCE
	AAR84398 ORF_03L Herpes simplex virus 1 strain R-15	SSPPPR
	CAA58413 U33 human herpesvirus 6 BAA78254 capsid protein human herpesvirus 6B	HCVL GMK
	CAA35376 HCMVUL61 human herpesvirus 5	GPPAP LP
	NP_044484 DNA packaging terminase subunit 1 human herpesvirus 2	Y+LRGAA
	NP_042966 DNA replication origin-binding helicase human herpesvirus 6	TI NGDF
	Q2HRD4 ORF4 human herpesvirus 8 type P (isolate GK18)	WDPPL KC
PICALM NP_001008660.1	AAR84403 ORF_08L Herpes simplex virus 1 strain R-15	TGSAVS
	ABX74960 dihydrofolate reductase-like protein Retroperitoneal fibromatosis-associated herpesvirus	SLTTAA-P
	CAA32311 very large tegument protein human herpesvirus 1	FD-LGGLL
	AAP88252 UL74 protein human herpesvirus 5	LKEQ-LK
	ABF22039 DNA polymerase catalytic subunit human herpesvirus 3	NPFLT--SG
	BAA86355 polyprotein Hepatitis C virus	FTPSPV
	NP_899479 hypothetical protein KVP40.0233 Vibrio phage KVP40	IRLFAA-YN+
	ADD94131 hypothetical protein uncultured phage MedDCM-OCT-S04-C1161	LKALKEQ-L
	NP_671655 EVM136 Ectromelia virus	SKTVCK T
	AAM92151AF436128_1 putative transforming protein E6 human papillomavirus—cand89	MVY-NERF
	YP_002727871 putative structural protein Pseudomonas phage phikF77	QYLA-RNT
	AAT73600 minor tail protein Lactococcus phage 943	STWGD FS
	BAE44071 polyprotein human coxsackievirus A24	TEKLLKT + II
	ADD25709 putative phage structural protein Lactococcus phage 1358	ATVDA DDAI
	NP_899479 hypothetical protein KVP40.0233 Vibrio phage KVP40	IRLFAA YN+
	YP_238567 ORF319 Staphylococcus phage Twort	ITTHHL--MV
	BAE44071 polyprotein human coxsackievirus A24	TEKLLKT-+--II
	YP_002332459 hypothetical protein PPMP29_gp34 Pseudomonas phage MP29	AL E Q LKALKE+

of sequences, this epitope has been used to label beta-amyloid in Alzheimer's disease brain [28] (Figure 2).

5. HSV-1 Proteins Bind to the Interaction Partners of *tau*

Because HSV-1 proteins are homologous to portions of the *tau* protein, one might expect the viral proteins to interfere with *tau* binding partners. This is indeed the case, as diverse herpes simplex viral proteins have been shown to bind to several of the interactome partners of *tau* (Table 6).

6. Discussion

Almost without exception, the genes encoding the proteins that match HSV-1 sequences (using the filter "Alzheimer") have been reported as genetic risk fac-tors in Alzheimer's disease (see http://www.polygenicpathways.co.uk/alzpolys.html) suggesting that such studies have been tracking HSV-1 (and other) infections over the years and inadvertently demonstrating that HSV-1 causes Alz-heimer's disease. This in no way detracts from the importance of these studies, but reflects a phenomenon that is probably common to most diseases. Because of our likely evolutionary

Table 6: The binding partners of *tau* (from the interaction section of NCBI gene) and their interaction with herpes simplex proteins (from the Wikigenes database) [11]; https://www.wikigenes.org/e/art/e/61.html.

Gene symbol	Name	Interaction with HSV-1 proteins
AATF	Apoptosis antagonizing transcription factor	—
ABL1	V-abl Abelson murine leukemia viral oncogene homolog 1	—
ACTB	Actin, beta	Virion component
APOE	Apolipoprotein E	Binds to glycoprotein B
BAG1	BCL2-associated athanogene	—
CALM1	Calmodulin 1 (phosphorylase kinase, delta)	Phosphorylated by ICP10
CAMK2A	Calcium/calmodulin-dependent protein kinase (CaM kinase) II alpha	—
CASP1	Caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase)	—
CASP3	Caspase 3, apoptosis-related cysteine peptidase	US3 phosphorylates procaspase 3
CASP6	Caspase 6, apoptosis-related cysteine peptidase	—
CASP7	Caspase 7, apoptosis-related cysteine peptidase	Activated during HSV-1 mediated apoptosis
CASP8	Caspase 8, apoptosis-related cysteine peptidase	Activity inhibited by LAT latency transcript
CDK1	Cyclin-dependent kinase 1	—
CDK5	Cyclin-dependent kinase 5	—
FLJ10357	Hypothetical protein FLJ10357	—
FYN	FYN oncogene related to SRC, FGR, YES	—
GSK3A	Glycogen synthase kinase 3 alpha	—
GSK3B	Glycogen synthase kinase 3 beta	Activated by HSV-1 infection
HSPA8	Heat shock 70 kDa protein 8	Recruited to nuclear domains following infection: ICP0 dependent
MAPK12	Mitogen-activated protein kinase 12	—
MAPT	Microtubule-associated protein *tau*	Phosphorylated by viral infection via GSK3B and PRKACA
MARK1	MAP/microtubule affinity-regulating kinase 1	—
MARK4	MAP/microtubule affinity-regulating kinase 4	—
OGT	O-linked N-acetylglucosamine (GlcNAc) transferase (UDP-N-acetylglucosamine:polypeptide-N-acetylglucosaminyl transferase)	—
PARK2	Parkinson disease (autosomal recessive, juvenile) 2, parkin	—
PHKG1	Phosphorylase kinase, gamma 1 (muscle)	—
PIN1	Protein (peptidylprolyl cis/trans isomerase) NIMA-interacting 1	—
PKN1	Protein kinase N1	—
PPP2CA	Protein phosphatase 2 (formerly 2A), catalytic subunit, alpha isoform	—
PPP2CB	Protein phosphatase 2 (formerly 2A), catalytic subunit, beta isoform	—
PPP2R5A	Protein phosphatase 2, regulatory subunit B′, alpha isoform	—
PPP5C	Protein phosphatase 5, catalytic subunit	—
PRKCD	Protein kinase C, delta	—
PSEN1	Presenilin 1 (Alzheimer disease 3)	—
RPS6KA3	Ribosomal protein S6 kinase, 90 kDa, polypeptide 3	—
RPS6KB1	Ribosomal protein S6 kinase, 70 kDa, polypeptide 1	—
S100B	S100 calcium binding protein B	—

Table 6: Continued.

Gene symbol	Name	Interaction with HSV-1 proteins
SNCA	Synuclein, alpha (non-A4 component of amyloid precursor)	—
SPTB	Spectrin, beta, erythrocytic (includes spherocytosis, clinical type I)	—
STAU1	Staufen, RNA binding protein, homolog 1 (Drosophila)	—
STUB1	STIP1 homology and U-box containing protein 1	—
STXBP1	Syntaxin binding protein 1	—
TUBA4A	Tubulin, alpha 4a	—
TUBB	Tubulin, beta	—
UBC	Ubiquitin C	Virion component
YWHAB	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, beta polypeptide	—
YWHAZ	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein, zeta polypeptide	Virion component

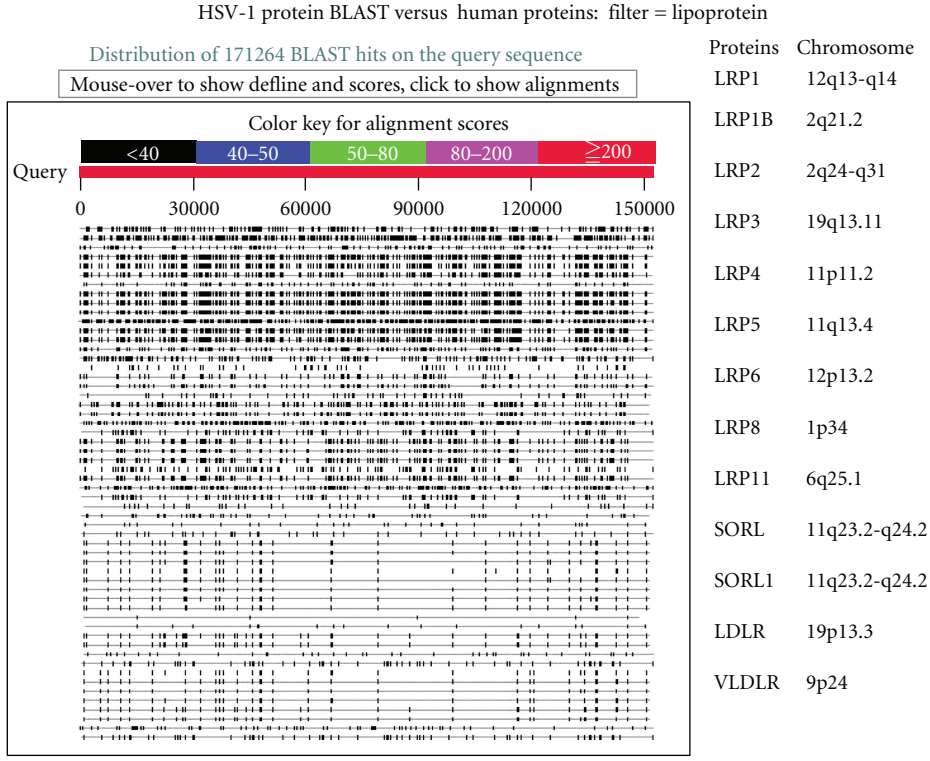


Figure 1: The BLAST result for HSV-1 proteins (translated viral genome versus human proteins) using the filter "lipoprotein." The repetitive patterns in the pictogram reflect homology with a number of different lipoprotein receptors located on different chromosomes, as shown in the table.

descent from viruses, first opined by J.B.S. Haldane and Francois D'Herelle almost a century ago [29, 30], our genomes contain traces of this descent which are transcribed into these short contiguous amino acid stretches (vatches) that exactly match many of the proteins in the current virome. Repeated viral insertions also add several genes to the human genome at once, a phenomenon that is likely responsible for evolutionary jumps, as suggested by others [31]. The idea that higher forms of life originated from viruses, although contentious, is supported by the fact that the entire human genome appears to be comprised of viral DNA. For example a BLAST of human chromosome 10 against all viral genomes (DNA versus DNA) returned 119,867 hits, covering the entire chromosome, with no gaps, in both inter- and intragenic regions (see http://www.polygenicpathways.co.uk/viralimages.htm). Similar results were obtained for other chromosomes. Our genomes and polymorphisms thus determine which vatches we possess, which viruses pose the threat, and which viral-related disease we are likely to develop. Whether we develop

the disease in question will depend on our encounters with the virus, whether we are vaccinated, and no doubt on our HLA-antigens and immune background related to the elimination of self-antibodies soon after birth.

This phenomenon appears to be universal, as vatches have been found in the XMRV virus, relating to human proteins involved in mitochondrial respiration and prostate cancer, in the Epstein-Barr virus, which matches multiple sclerosis autoantigens [27], in the AIDS virus which targets vatches in over 50 components of the human immune network, in the papillomavirus which targets cervical cancer oncogenes, and in the HSV-2 virus which targets schizophrenia susceptibility gene products (see http://www.polygenicpathways.co.uk/BLASTS.htm). It is even relevant to human genetic diseases as the polyglutamine repeats observed in Huntington's disease and spinocerebellar ataxias align with very common viruses (the ubiquitous HHV-6) while the cystic fibrosis mutant aligns with pseudomonas and staphylococcal phages, whose bacterial hosts have been found to shorten the lifespan of these patients. The London mutation in Alzheimer's disease converts the surrounding peptide to a vatch that is homologous to proteins from the rhinoviruses that cause the common cold [26, 27, 32, 33]. Every human protein so far screened by the author, without a single exception, displays this type of homology to particular but specific sets of virus for each protein. Similarly all viruses so far screened (~30) express proteins with homology to a large but specific subset of human proteins.

These viral homologues may interfere with Alzheimer's disease pathological pathways in a number of ways. Firstly, as demonstrated by the complement receptor 1 HSV-1 viral mimic, the viral protein can substitute for its human counterpart, presumably diverting its function towards different compartments. Secondly, as they are clearly able to substitute for their human counterparts, they are likely to interfere with their protein/protein networks (interactome). This was clearly demonstrated for *tau*, where herpes simplex virus proteins do indeed bind to *tau* binding partners.

As many of these matching sequences are highly immunogenic, antibodies to the virus may also target the human homologue, in effect producing a protein knockdown and reproducing the effects, but on a massive scale, seen in various Alzheimer's disease-related knockout mice [34–39]. Such immunogenic viral proteins may also generate antibodies capable of mounting an immune attack against their human counterparts, killing the cells in which they reside by immune and inflammatory mechanisms, and by complement-related lysis (see below).

7. The Dangers of Autoimmunity

The immunogenic profile of some of these homologues may also be responsible for the neurodegeneration and pathological features observed in Alzheimer's disease. Antibodies to the human proteins may result in immune, inflammation, and complement pathway activation, killing the cells in which the human homologue resides. There is a great deal of evidence supporting autoimmune attack in the Alzheimer's disease brain.

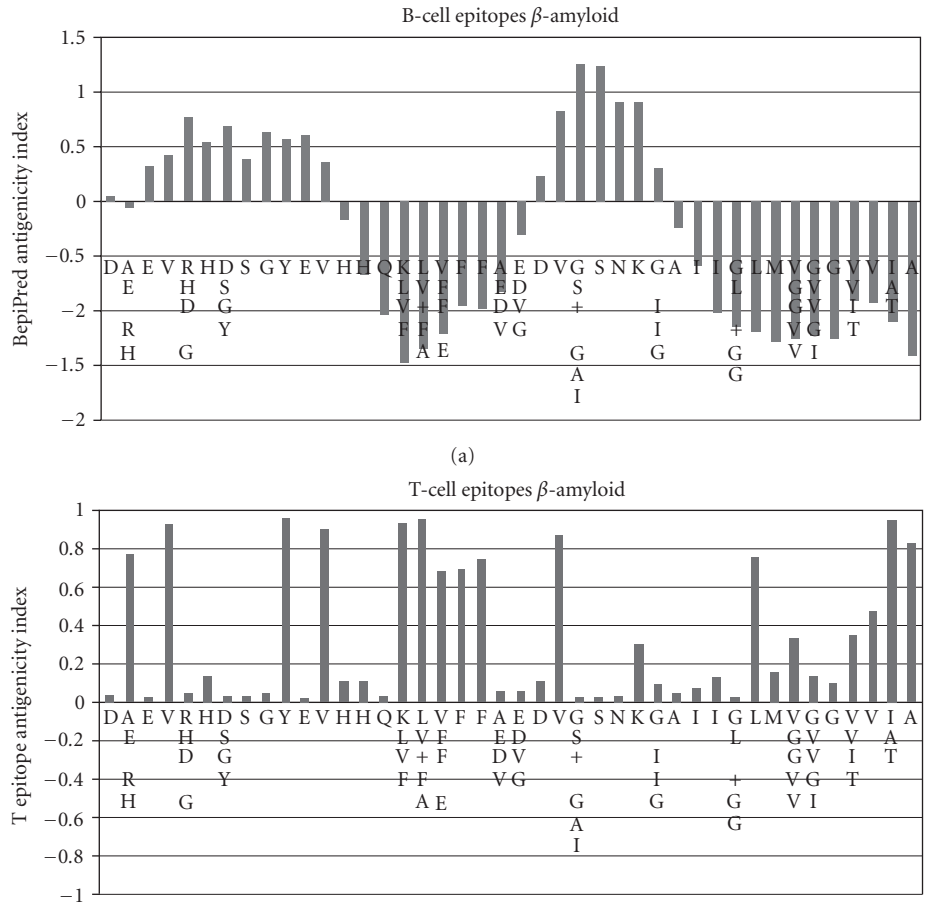
A number of immune-system-related proteins are found in amyloid plaques or neurofibrillary tangles. Interleukin 1 alpha, interleukin 6, and tumour necrosis factor are all been localised within plaques, and acute phase proteins involved in inflammation, such as amyloid P, alpha-1 antichymotrypsin, and C-reactive protein are also plaque components while immunoglobulin G is located in the plaque corona [14, 40–42]. Large increases in IgG levels have been recorded in the brain parenchyma, in apoptotic dying neurones, and in cerebral blood vessels in the Alzheimer's disease brain [43]. Complement component C3 is found in Alzheimer's disease amyloid plaques along with complement C4 [44]. Complement components Clq, C3d, and C4d are present in plaques, dystrophic neuritis, and neurofibrillary tangles [45].

The membrane attack complex (MAC), composed of complement proteins C5 to C9, forms a channel that is inserted into the membranes of pathogens, destroying them by lysis. These components cannot be detected in temporal cortex amyloid plaques in Alzheimer's disease [41, 44, 46]. However the MAC complex is present in dystrophic neurites and neurofibrillary tangles [45], and others have detected this complex in neuritic plaques and tangles, along with deposition of C1q, C3, and clusterin [47]. The membrane attack complex has also been detected in the neuronal cytoplasm in AD brains and associated with neurofibrillary tangles and lysosomes [46].The presence of the MAC complex in neurones might suggest that neuronal lysis by the MAC complex could contribute to neuronal cell death [45].

The microtubule protein *tau* was one of the more antigenic proteins revealed in this survey and one with numerous matches to herpes viral proteins that would be equally immunogenic. Immunisation with *tau* in mice produces tauopathy, neurofibrillary tangles, axonal damage, and gliosis [48] demonstrating the dangers of autoimmunity in a manner directly relevant to Alzheimer's disease.

Beta-amyloid autoantibodies are common in the ageing population and in Alzheimer's disease and may be related to herpes simplex and numerous other viruses or phage proteins that exactly vatch a VGGVV C-terminal sequence in beta-amyloid that is immunogenic. The epitope for this sequence labels beta-amyloid in the Alzheimer's brain [28]. This pentapeptide is, *per se*, fibrillogenic [49]. This is a characteristic of both beta-amyloid and of HSV-1 glycoprotein B peptide fragments containing this sequence. The viral glycoprotein B fragments form thioflavin T positive fibrils which accelerate beta-amyloid fibril formation and are neurotoxic in cell culture [50]. Other stretches of beta-amyloid are homologous to a diverse set of viral, bacterial, fungal, and allergenic proteins, likely providing the source of the autoantibodies in the ageing population [32].

Antibodies to beta-amyloid have been suggested as a therapeutic option in Alzheimer's disease. The potential use of beta-amyloid antibodies is based on their ability to reduce plaque burden and neurite dystrophy in APP transgenic mice [51]. Several studies have demonstrated that beta-amyloid antibodies reduce plaque burden in APP transgenic models and that they can also improve cognitive



(a)

VGGVV: Aeromonas phage, Allpahuayo virus, Clostridium phage, Dengue virus, Ectromelia virus, Enterobacteria phage, Escherichia phage, Feline Calicivirus, Haemophilusphage, Halomonas phage, Hepatitis C , Hepatitis delta, HHV-6, HHV-6B, HSV-1, HSV-2, Human coronavirus, Human enterovirus, Human immunodeficiency virus 1, Human adenovirus 8, Iguape virus, Infectious bronchitis virus, Lactate dehydrogenase-elevatin g virus, Lactococcus phage, Microcystis phage, Mycobacterium phage, Polyomavirus HPyV7, Prochlorococcus phage, Pseudomonas phage, Roseophage, Salmonella phage, Shigella phage, Streptococcus,phage, Synechococcus phage, Variola virus, Vibrio phage, Viral hemorrhagic septicemia virus, Yellow fever

(b)

Figure 2: The B cell and T cell immunogenicity profile for the beta-amyloid peptide. According to the servers, antigenicity values of >0.35 (B cell) or 0.5 (T cell) are considered immunogenic. The sequences of herpes simplex viral proteins that align with beta-amyloid are shown. Space: non-identical amino acid; +: conserved amino acid with similar physicochemical properties. Viruses and phages containing the VGGVV sequence, which has been used as an epitope to label beta-amyloid in Alzheimer's disease, are also shown.

performance [52]. However amyloid antibodies extracted from the serum of old APP transgenic mice potentiate the toxicity of beta-amyloid, and Alzheimer's disease patients display an enhanced immune response to the peptide [53]. Again in transgenic mice, different immune backgrounds can influence the type of immune responses elicited by beta-amyloid. For example, B and T cell responses to beta-amyloid can be modified in HLA-DR3, -DR4, -DQ6, or -DQ8 transgenic mice [54]. HLA-antigen diversity in Man is also likely to determine the outcome of beta-amyloid/antibody interactions. A large number of Alzheimer's disease susceptibility gene candidates, including clusterin and complement receptor 1, as well as diverse interleukins and other cytokines, C reactive protein, HLA-antigens, Fc epsilon and Toll receptors, and the viral-activated kinase PKR, are intimately concerned with pathogen defence and or the immune system, supporting a genetic contribution to the immune pathogenesis of Alzheimer's disease (see http://www.polygenicpathways.co.uk/alzpolys.html.)

Beta-amyloid vaccination in Alzheimer's disease (against $Abeta_{1-42}$) has so far not been successful and sadly resulted in meningoencephalitis and the death of a patient [55]. While certain beta-amyloid antibodies may reduce plaque burden, there is an evident risk that they may also trigger an autoimmune response, potentially killing beta-amyloid containing neurones. Catalytic autoantibodies are less able

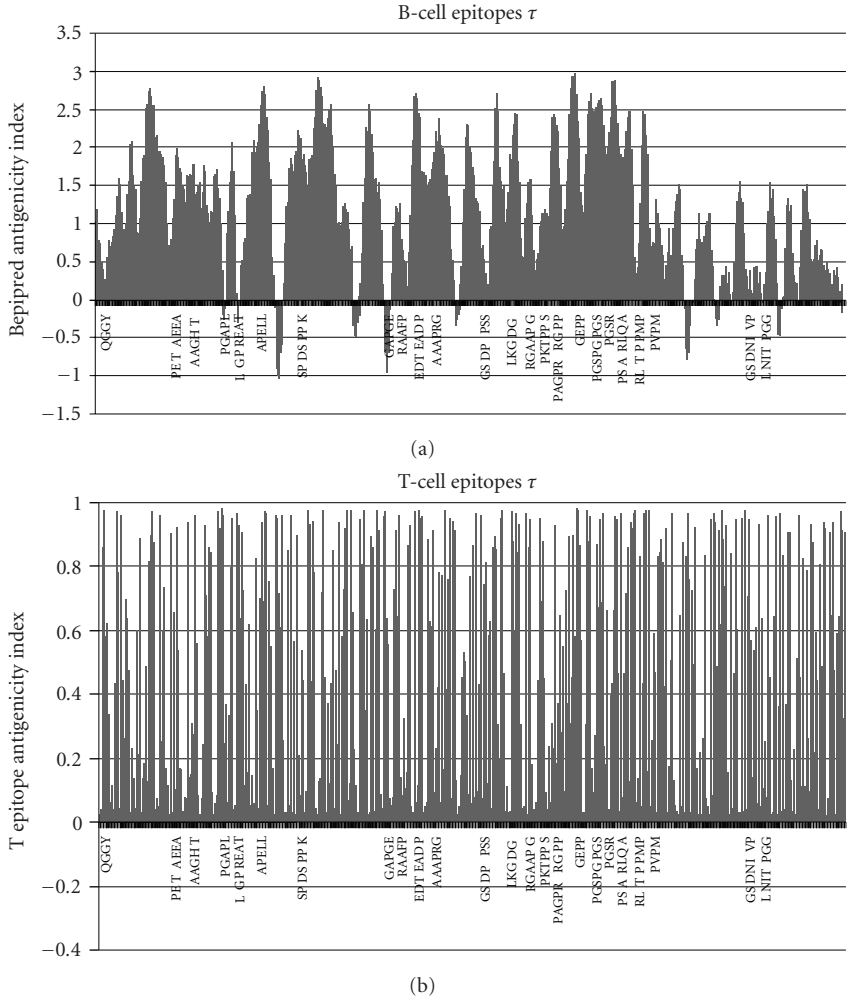


Figure 3: The B cell and T cell immunogenicity profile for the *tau* protein. The sequences of herpes simplex viral proteins that align with *tau* are shown. Space: non-identical amino acid; +: conserved amino acid with similar physicochemical properties.

to form stable immune complexes and likely represent the safest way forward in this area [56, 57]. Given the homology of beta-amyloid to so many viruses and the potential dangers of autoimmunity, as well as the clearly toxic effects of *tau* immunisation, the pursuit of clinical trials with beta-amyloid antibodies, with the exception of catalytic forms, must surely be questioned.

8. Conclusions

Alzheimer's disease proteins encoded by all of the major genetic players in Alzheimer's disease and many other relevant proteins are homologous to proteins from the herpes simplex virus, confirming the implication of this virus as a causative agent in this disease [48, 50, 58–70]. Because of homology to other viruses and pathogens, these too may be implicated. These include HHV-6, the cytomegalovirus, Borrelia, Burgdorferi, Chlamydia Pneumoniae, Helicobacter pylori, Cryptococcus neoformans and bacteria promoting gum disease, such as P. Gingivalis, all of which also express proteins homologous to the products of numerous Alzheimer's disease susceptibility genes (see http://www.polygenicpathways.co.uk/Alzheimer.htm).

No vaccine against HSV-1 exists, but in the long term, may perhaps be able to prevent Alzheimer's disease, although the potential dangers of vaccine-related autoimmunity evidently need to be addressed. Interestingly, cancer-causing viruses including the Epstein-Barr-virus, hepatitis b, and the papillomavirus align with the peptide stretch within beta-amyloid [32] that is cleaved by the beneficial catalytic autoantibodies to beta-amyloid [56, 57]. Cancer is inversely associated with the risk of developing Alzheimer's disease [71, 72]. As a vaccine to the human papillomavirus already exists to prevent cervical cancer [73], it may well have a role to play in the prevention or therapy of Alzheimer's disease, again with due regard to the problem of vaccine-related autoimmunity. Alternatively, immunisation with this beneficial region of the beta-amyloid peptide might be considered as a viable therapeutic option.

Many of the toxic effects of HSV-1 infection are likely to be related to autoimmunity, caused by antibodies to the viral proteins that also target their human counterparts. In this case, it is possible that immunosuppressant therapy

may be of benefit in Alzheimer's disease patients and also that aggressive antiviral therapy should be pursued. Immunoadsorption of *tau* and beta-amyloid antibodies, a technique used to good effect in certain patients with myasthenia gravis (characterised by autoantibodies to nicotinic receptors) [74] may also be of benefit. As other pathogens may also demonstrate this type of mimicry, detailed and regular pathogen screens in the ageing population and in the early stages of Alzheimer's patients may also be of use.

Alzheimer's disease thus appears to be one, probably of many, "pathogenetic" diseases, caused by viruses and other pathogens, but dependent on our genes, which dictate the protein sequences that match those in particular subsets of pathogen proteins. There are almost 3,000 viral genomes in the NCBI database, probably reflecting but a small proportion of those existing on the planet. In addition, as viruses regularly mutate with replication there are likely to be multiple strains of HSV-1 (and other viruses), only one of which is recorded in the NCBI database. Nevertheless, with current bioinformatics techniques, it should be possible to rapidly identify all vatches in the human proteome, to match them to particular viruses (and other pathogens, Bacteria, fungi, yeast, parasites, etc.), and to pair these with diverse human diseases. Our understanding of this universal phenomenon could radically change the face of therapy in a variety of human conditions.

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