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Research Article

Schizophrenia: A Pathogenetic Autoimmune Disease Caused by Viruses and Pathogens and Dependent on Genes

C. J. Carter

Polygenic Pathways, 20 Upper Maze Hill, St Leonards-on-Sea, East Sussex, TN38 OLG, UK

Correspondence should be addressed to C. J. Carter, chris_car@yahoo.com

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Many genes have been implicated in schizophrenia as have viral prenatal or adult infections and toxoplasmosis or Lyme disease. Several autoantigens also target key pathology-related proteins. These factors are interrelated. Susceptibility genes encode for proteins homologous to those of the pathogens while the autoantigens are homologous to pathogens' proteins, suggesting that the risk-promoting effects of genes and risk factors are conditional upon each other, and dependent upon protein matching between pathogen and susceptibility gene products. Pathogens' proteins may act as dummy ligands, decoy receptors, or via interactome interference. Many such proteins are immunogenic suggesting that antibody mediated knockdown of multiple schizophrenia gene products could contribute to the disease, explaining the immune activation in the brain and lymphocytes in schizophrenia, and the preponderance of immune-related gene variants in the schizophrenia genome. Schizophrenia may thus be a "pathogenetic" autoimmune disorder, caused by pathogens, genes, and the immune system acting together, and perhaps preventable by pathogen elimination, or curable by the removal of culpable antibodies and antigens.

1. Introduction

Over 600 genes have been implicated in schizophrenia in association studies, supporting the contention that multiple genes of small effect contribute to this condition [1, 2] (see http://www.polygenicpathways.co.uk/schizgenesandfunc.htm for association references). These genes cluster together in clearly defined signalling networks related to the diverse subpathologies of schizophrenia [3–7]. Epistasis between genes within these same signalling networks markedly affects the degree of risk-promotion [8–10], in part, explaining the inconsistency in genetic association studies.

Schizophrenia has also been associated with prenatal complications including maternal rubella (German measles) [11], influenza [12, 13], Varicella zoster (chicken pox) [14], Herpes (HSV-2) [15], common cold infection with fever [16], or poliovirus infection [17] while in childhood or adulthood, coxsackie virus infection (in neonates [18]) or Lyme disease (vectored by the Ixodes tick and Borrelia Burgdorferri) or Toxoplasmosis have been reported as risk factors [19, 20] (see Table 1). The human endogenous retrovirus, HERV-W, has also been implicated in schizophrenia [21]. A number of schizophrenia-related genes are implicated in the life cycles of these pathogens, suggesting an interplay between genes and risk factors [22].

Many schizophrenia genes relate to the immune network [5, 6, 22, 23]. Immune activation is also observed in the schizophrenic brain [24, 25] or in lymphocytes [26–29]. A number of autoantigens/autoantibodies to key schizophrenia-related proteins have also been reported. These include dopamine, serotonin, acetylcholine, and NMDA receptors; inter alia (Table 2). Maternal immune activation in animal models has also been shown to generate phenotypes relevant to schizophrenia in the offspring [30].

As shown below, genes, risk factors, and immunity can be linked together forming a unifying pathway whose elements are interdependent. Dysfunction of this network which is conditional upon interactions between its three branches may be responsible for schizophrenia.

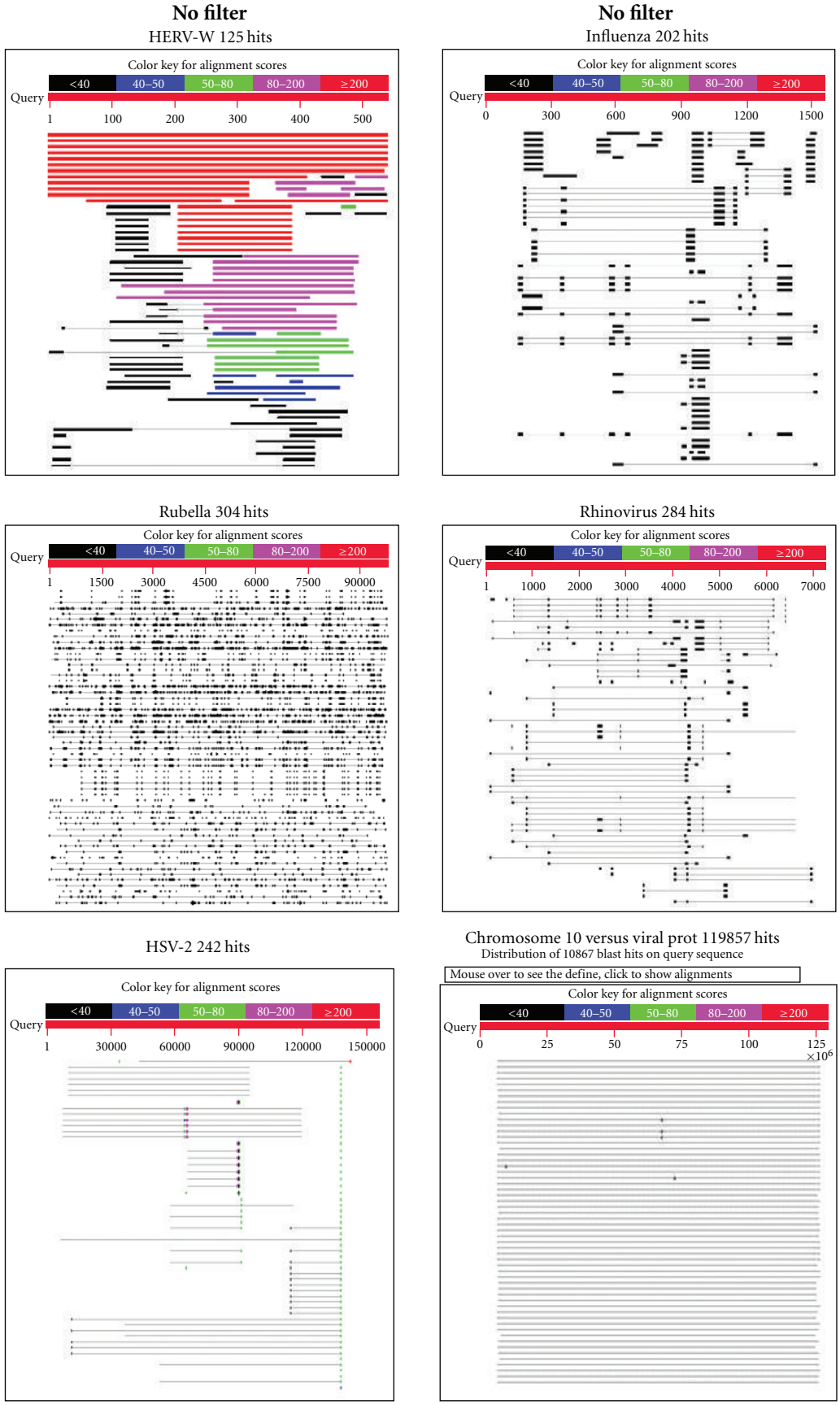

Figure 1: Continued.

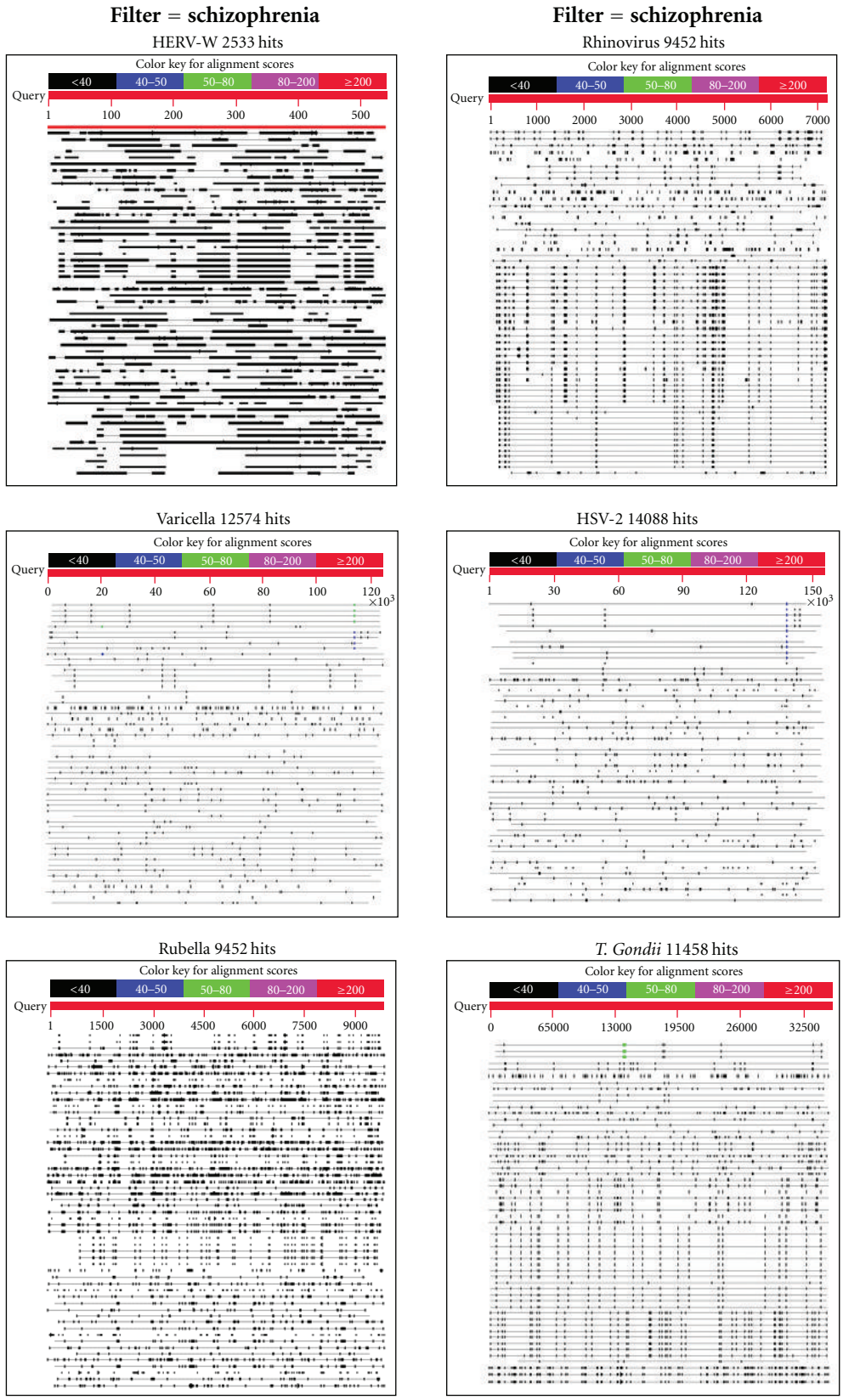

Figure 1: Screenshots of the pictorial representation of the viral BLAST results against the human proteome. The streaks dotted throughout the human genome/proteome represent the areas of homology, some with contiguous sequences of 5 or more amino acids. The number of hits is shown for each virus or pathogen. The figure also shows the total coverage of human chromosome 10 by viral gene homologues. The top set of figures were from unfiltered blasts while the bottom set of 6 figures represent filtered blasts using the query "schizophrenia".

The larger font illustrates highly antigenic regions of DISC1 (and of the viral homologues). The boxes represent the alignment position and the blue letters 100% identity.

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>gi|61742823|ref|NP_061132.2| disrupted in schizophrenia 1 protein isoform L [Homo sapiens]
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(a) Varicella virus vatches within DISC1

The larger font illustrates highly antigenic regions of DISC1 (and of the viral homologues).

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>gi|61742823|ref|NP_061132.2| disrupted in schizophrenia 1 protein isoform L [Homo sapiens]
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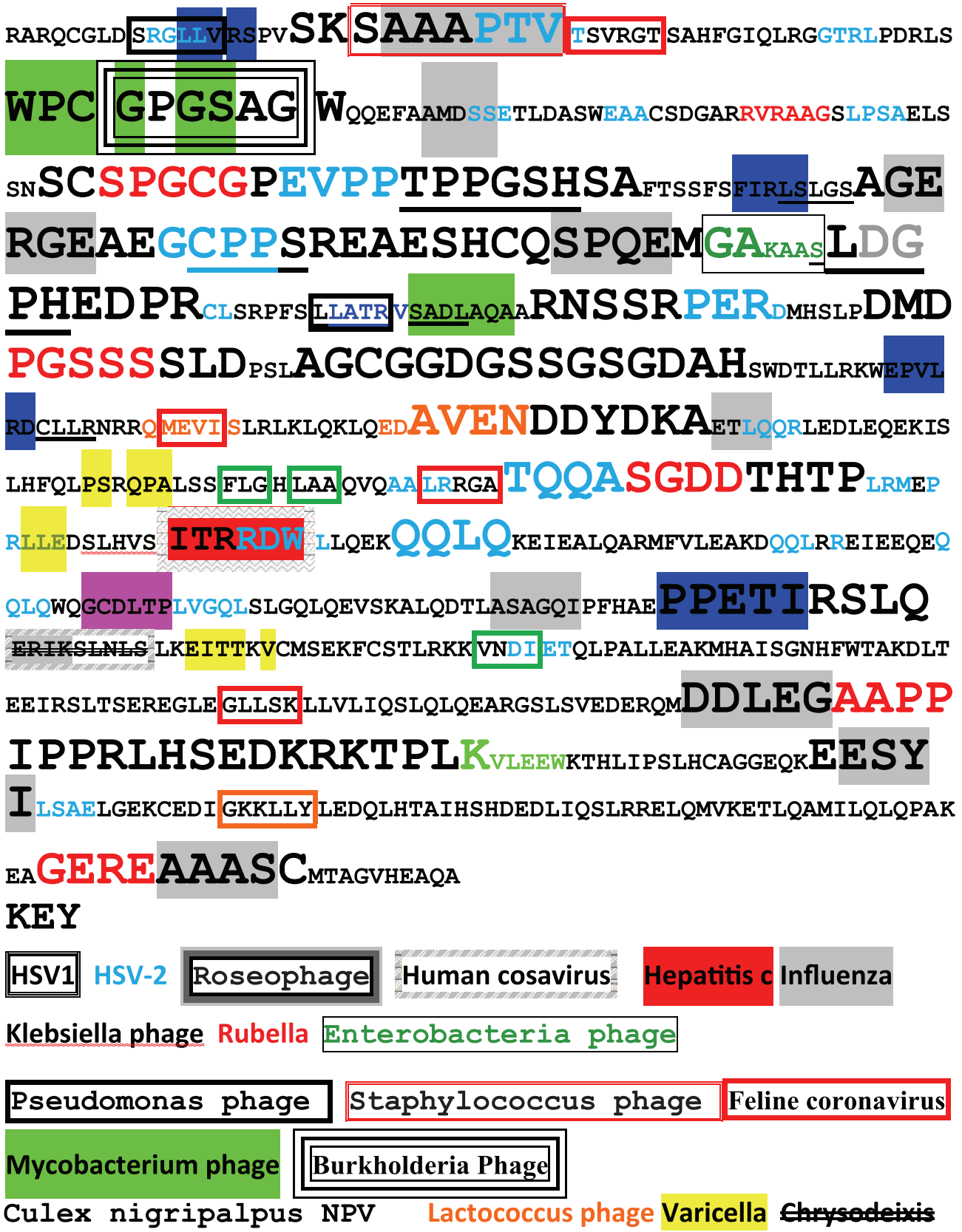
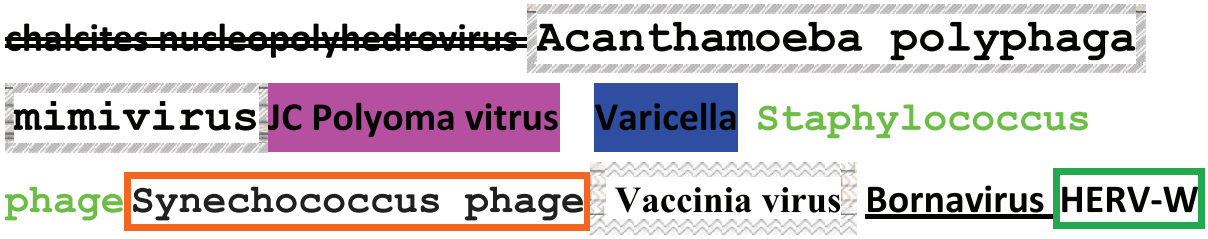
(b)

Figure 2: Continued.



(b)

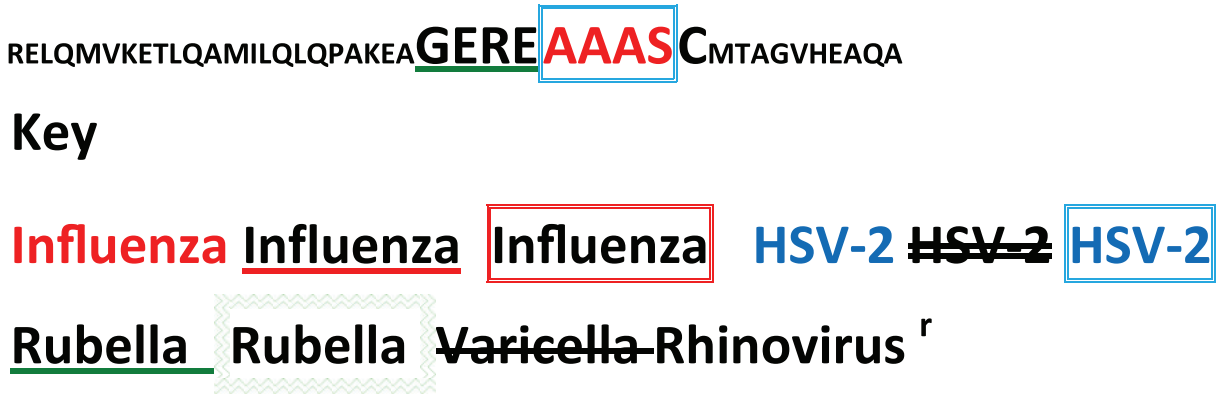
Figure 2: Continued.



(b) Multiple virus vatches within DISC1

(c)

Figure 2: Continued.



(c) The homology of viral risk factors to the highly antigenic regions of DISC1 (and of the viral homologues)

Figure 2: (a) Varicella protein alignments within DISC1: the boxed regions show the region of alignment, and the blue letters denote 100% identity. This is not an alignment of the whole Varicella proteome but represents fragments of the same or different Varicella proteins that align with DISC1 fragments (vatches). The larger font delineates highly antigenic regions of DISC1 with an antigenicity index of >0.8 (Figure 4). (b) Other viral vatches within the DISC1 protein. The vatches are colour or format coded in relation to the different viruses. (c) Viral vatches for the risk factors implicated in schizophrenia in relation to the highly immunogenic regions of DISC1.

2. Methods

The human herpesvirus 2 genome (NC_001798) as well as those of the rhinovirus (NC_001490), rubella (NC_001545.1) and Varicella zoster (NC_001348.1) and HERV-W (NP_055405.3: env polyprotein) viruses, Borrelia Burgdorferi (NC_011728) and T. Gondii (NC_001799: Partial genome) were screened against the human proteome using the NCBI BLAST server and the Entrez query filter "schizophrenia". The HERV-W, influenza, HSV-2 and rubella viruses were also screened unfiltered (Translated pathogen genome versus human proteins: BlastX) [31]. The BLAST algorithm detects overall homology between entire gene or protein sequences, and it is necessary to set parameters to low significance levels in order to detect short intraprotein consensus homology. The parameters used were: Expect 20,000, E value = 100,000; matrix PAM30. The original BLAST results are stocked at http://www.polygenicpathways.co.uk/blasts.htm. Information for all abbreviations is available at this site, provided by the NextBio highlighting service.

BLAST files were scanned by an online tag cloud generator producing tags sized according to gene word occurrences http://www.tagcloud-generator.com/generator.php#anker. Word occurrences were counted using a "Highlightall add-in" for Firefox https://addons.mozilla.org/en-US/firefox/addon/4240/.

Antigenicity (B-cell epitope prediction) was estimated using the BepiPred server http://www.cbs.dtu.dk/services/BepiPred/[32] (Table 4).

Kegg pathway analysis [33] of 632 schizophrenia susceptibility gene candidates was performed using Kegg mapper http://www.genome.jp/kegg/tool/color_pathway.html. The results of this analysis are available at http://www.polygenicpathways.co.uk/keggszgenes.htm. Venn diagrams were constructed online at http://www.bioinformatics.org/gvenn/index.htm[34].

Genes and risk factors with at least one positive association are included in this study. Although certain genes and risk factors are clearly more important than others, and problems of replication in both gene and risk factor studies abound, gene, gene, and gene/environment interactions may explain some of the heterogeneity. For example many schizophrenia-related genes are involved in the life cycle of T. Gondii, but may be irrelevant if this pathogen is not encountered. Similarly T. Gondii infection may have little effect is such gene variants are not present. Pathway analyses of genome wide association data, and previous studies, are showing that the risk-promoting effects of many genes in similar pathways are better predictors of risk, than when treating each gene in isolation (see Section 1). Although some of these factors may be false positives, many genes and risk factors may have a role to play in certain conditions, but the greater import of genes such as DISC1 or neuregulin is recognised.

3. Results

Pictograms of selected BLAST results are shown in Figure 1. The initial sweep of unfiltered BLASTs returned 125–304 hits, but this number was markedly increased when using the filter "schizophrenia" (14,088 Hits for HSV-2). For unfiltered sweeps, the viral homologues are longer, while the filtered sweeps return shorter contiguous sequences nevertheless including multiple matches of pentapeptides or more.

Viral-human matches are characterised by short contiguous amino acid matches of 5 or more amino acids, that are identical in viral and human proteins, defined as vatches (viral matches). These are exemplified, for DISC1 in Figure 2. Hexapeptide matches have also been described for the influenza H5N1 virus and this study also highlighted homologies with DISC1, reelin and neurexin, inter alia [35]. The entire length of a human protein can be composed of

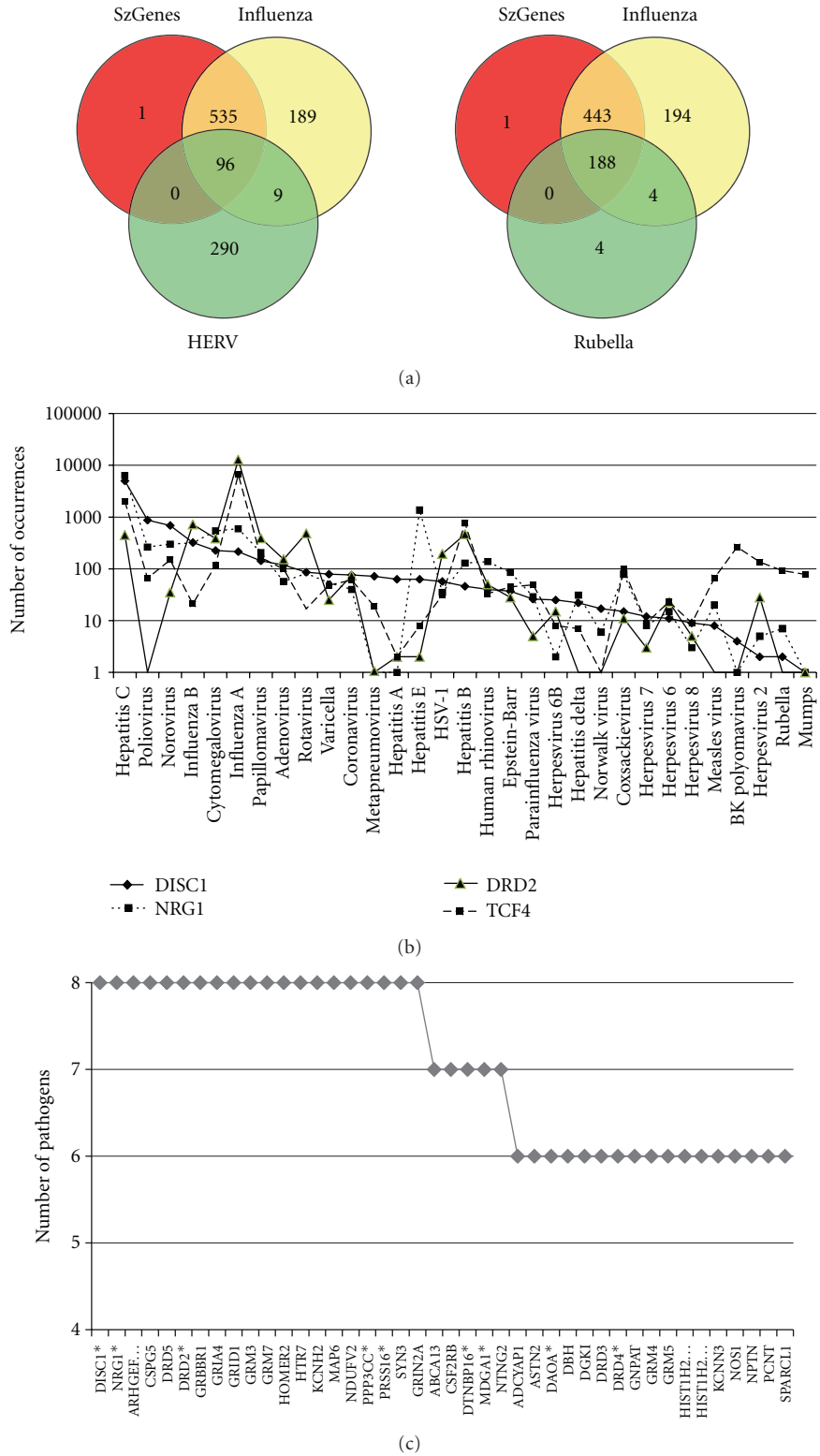


Figure 3: (a) Venn diagrams of the number of Schizophrenia gene products ($N = 632$) with homology to the rubella, HERV-W and influenza viruses. The singleton in SZ-genes was different on each occasion: Thus, all genes are covered. (b) The viral matching spectra of DISC1, neuregulin, the dopamine D2 receptor and transcription factor 4. The Y-axis depicts the number of word occurrences on the original BLAST results page. Note the logarithmic axis. (c) The number of pathogens expressing proteins with homology to the protein products of schizophrenia susceptibility genes. Those marked by an asterisk are within the 30 top-ranked genes in SZ-gene http://www.szgene.org/.

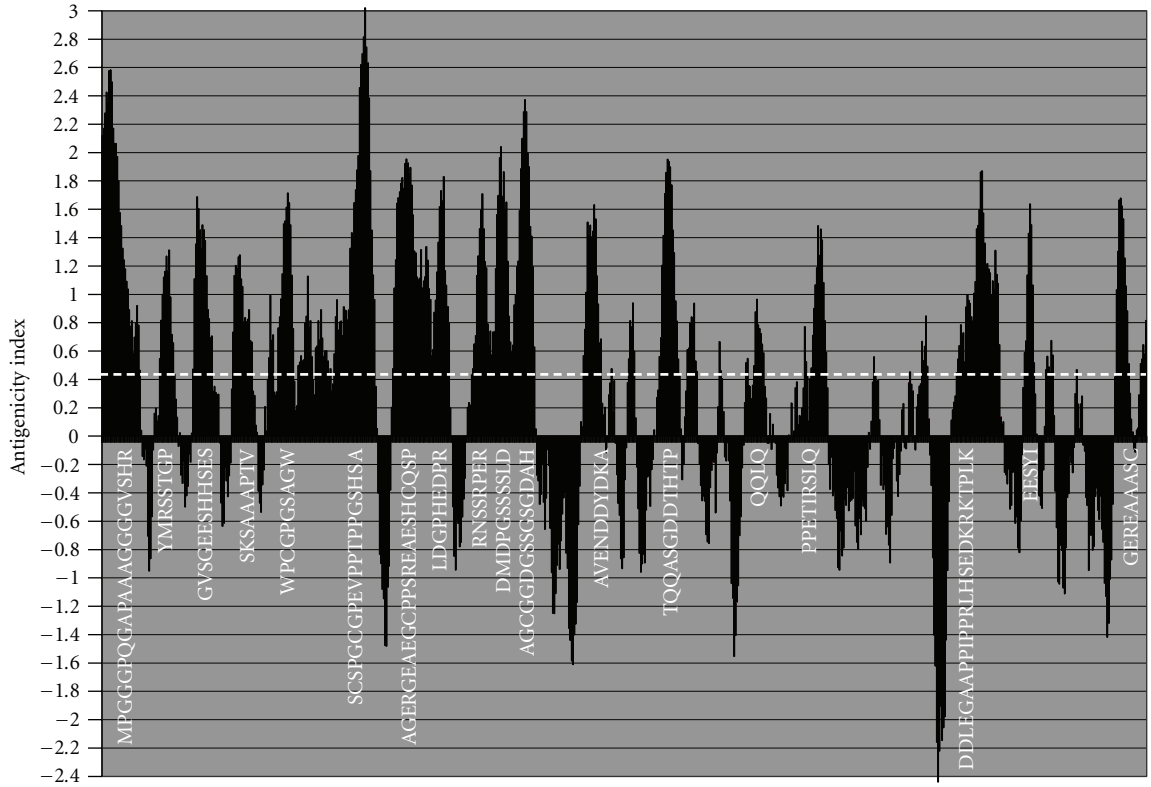


Figure 4: The antigenicity (B-cell epitope prediction) of DISC1: the amino acid sequences with an index of >0.35 are considered as epitopes. A value of 0.8 was chosen to define highly antigenic regions as seen in Figure 2. The amino acid sequences of these highly antigenic regions are shown.

many overlapping, intercalated vatches, related to multiple viral species. However, the viral spectrum is distinct for each protein as shown in Figure 3 for DISC1, neuregulin, the D2 dopamine receptor and transcription factor 4. Each is homologous to proteins from a large spectrum of viruses, but this spectrum is distinct for each protein. Interestingly, all are homologous to proteins from the hepatitis C virus. Several studies have noted that Hepatitis C infection is associated with schizophrenia, but this has generally been interpreted in terms of a schizophrenia life style that favours infection, rather than viewing Hepatitis C as a risk-promoting factor [36–39]. These data may challenge this assumption.

All of the pathogens implicated in schizophrenia express proteins with homology to multiple schizophrenia susceptibility gene products (Table 3). The profile of each individual pathogen is again specific for different types of gene product, but all target key members of the schizophrenia network including dopamine, serotonin and glutamate receptors as well as neuregulin and growth-related or DISC1 related pathways. This is the case even when no filter is used. Interestingly, both the rubella and the influenza viruses target members of the translation initiation complex, which has been implicated in myelination and oligodendrocyte survival [4, 40]. Oligodendrocyte cell loss and myelination defects are prominent in the schizophrenic brain [41–44].

The degree of overlap between the rubella, HERV and influenza viruses and schizophrenia gene products is shown by the Venn diagrams in Figure 3. All but one schizophrenia gene product was covered by various permutations and similar data were recovered for other pathogens. All schizophrenia gene products ($N = 632$) were homologous to proteins expressed by one or more of these pathogens. However, only 16 proteins were common to all 8 pathogens (Figure 3). These included neuregulin (NRG1) and DISC1, dopamine (DRD5), glutamate (GRIA4, GRID1, GRM3, GRM7) GABA (GABBR1) and serotonin (HTR7) receptors, a presynaptic protein regulating glutamate release (synapsin SYN3) and HOMER2, a member of the postsynaptic scaffold, all of which are key elements relating to the pathology of schizophrenia.

Other proteins within this class included neurocan (CSPG5), a chondroitin sulphate proteoglycan expressed in oligodendrocytes that inhibits neurite outgrowth and regulates axonal growth [45–47]. It is also involved thalamocortical projection development [48]. ARHGEF10 is a rho Guanine-nucleotide exchange factor that controls myelination [49]. NDUFV2 is a subunit of the mitochondrial respiratory chain and its protein expression levels are reduced in the frontal cortex and striatum in schizophrenia [50]. PPP3CC Calcineurin gamma (PPP3CC) plays a role in dopamine receptor signalling [51, 52]. Calcineurin knockout mice show defects in prepulse inhibition and other phenotypes related to schizophrenia [53]. Calcineurin is highly expressed in the immune system and regulates the expression of numerous

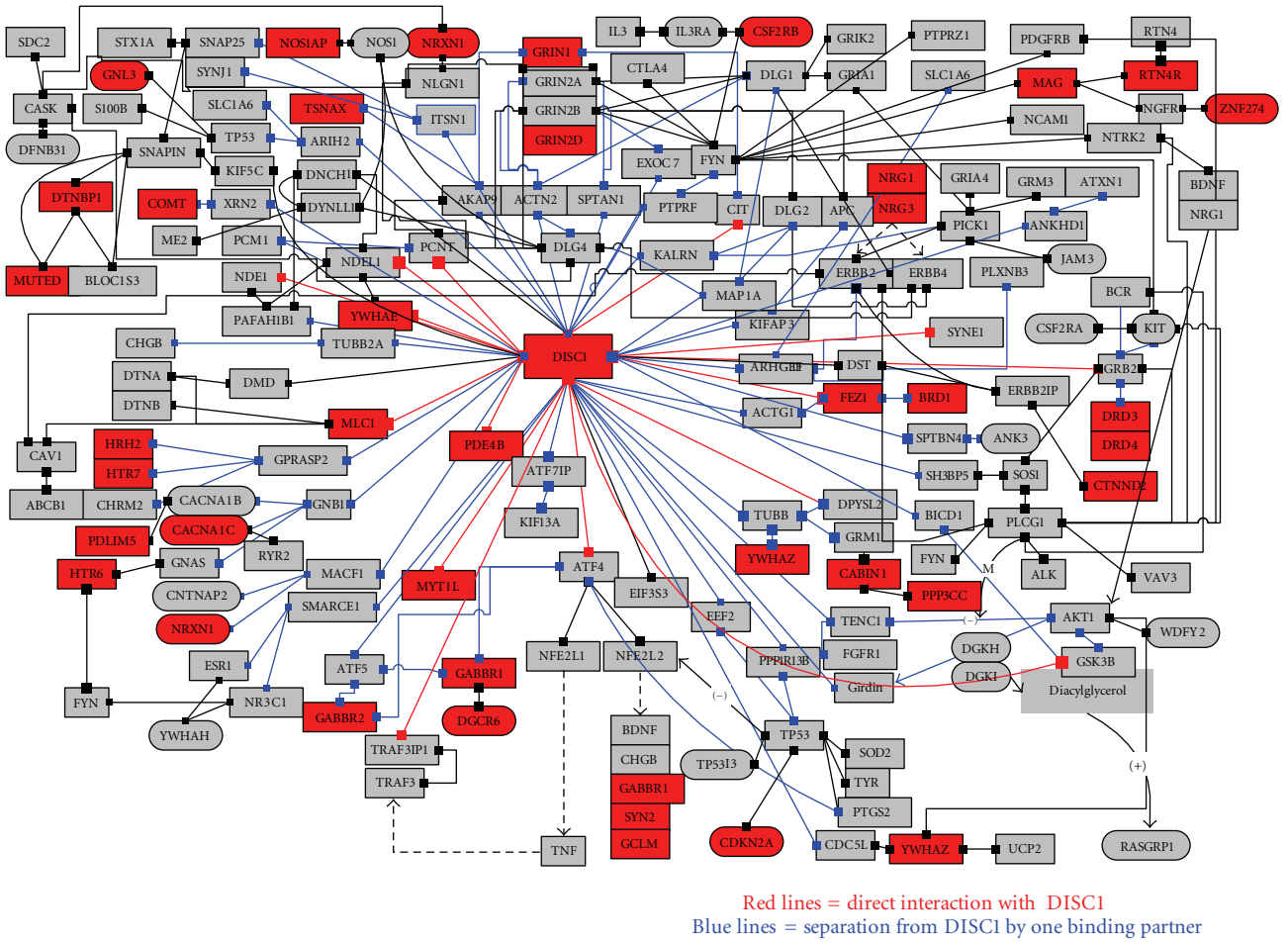


FIGURE 5: The DISC1 interactome see http://www.polygenicpathways.co.uk/discforum.htm. Proteins in red are homologous to Rubella proteins.

cytokines [54]. MAP6 is a microtubule protein that controls synaptic organisation, in particular of glutamatergic synapses where it controls the expression of the glutamate transporter and presynaptic genes, synaptophysin and GAP-43, spinophilin and MAP2. [55, 56] KCNH2 is a potassium channel that plays a role in the development of neural crest cells [57] and in lymphocyte proliferation [58]. PRSS16 is a serine protease involved in autoimmunity and the presentation of self-antigens within the thymus [59].

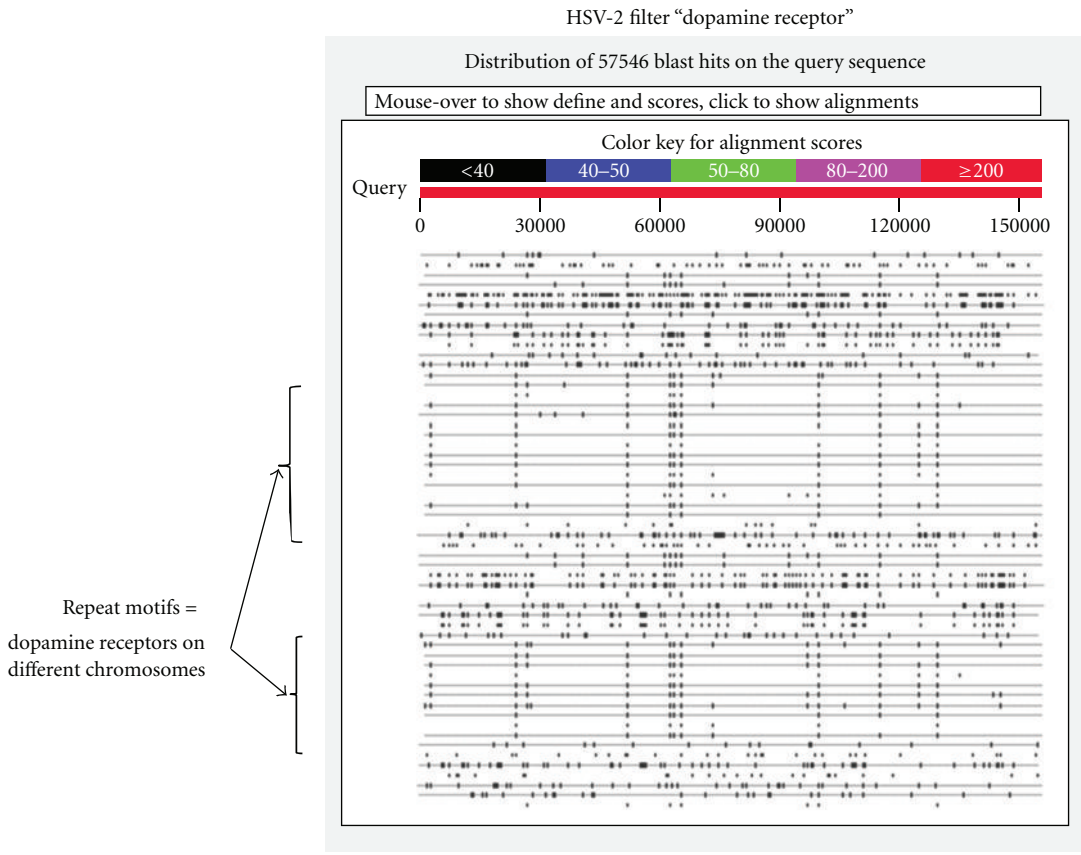
So, by a random bioinformatics process, trawling the entire human proteome, asking simply which proteins are homologous to those of the pathogens implicated in schizophrenia, we arrive at a small set of proteins related to synaptic and dendritic function, myelination, neuregulin and DISC1 pathways, glutamate, dopamine, GABA and serotonin transmission, and immune regulation that are the cornerstones of schizophrenia pathology [3, 60–62].

3.1. Autoantigens in Schizophrenia. Many autoantibodies have been reported in schizophrenia. The pathogens implicated in schizophrenia also express proteins that are homologous to these autoantigens. Again the profile of each autoantigen or pathogen is distinct as shown in Table 2.

3.2. DISC1. DISC1 is a key "hub gene" in schizophrenia linked, via its interactome, to many other schizophrenia susceptibility gene products [3, 63–66]. Its viral homology is illustrated in Figure 2. The Varicella virus is homologous to DISC1 in several regions, over its entire length, many matches in regions of high immunogenicity. These figures illustrate the types of matches seen in other proteins and shows that the vatches are often part of larger gapped consensus sequences. Interestingly, Varicella infection also results in the production of antibodies to pericentrin, a DISC1 binding partner [67].

DISC1 is a highly immunogenic protein, as predicted by B-cell epitope prediction (Figure 4). Autoantibodies to DISC1 have not been reported in schizophrenia. However, the viral risk factors implicated in schizophrenia express proteins that are homologous to the highly antigenic regions of the DISC1 protein, as shown in Figure 2. These viral proteins are equally antigenic and antiviral antibodies might also thus be expected to target multiple regions of the DISC1 protein.

3.3. Viral Proteins Are Part of the DISC1 Interactome. DISC1 and many of its binding partners, or other members of



Glutamate	Dopamine	Serotonin	GABA	Acetylcholine	Other
NMDA	DRD2 11q23	HRTR1A	GABRA1	CHRM5	CCKAR
GRIN2A	DRD3 3q13.3	HTR2A	GABBR1	CHRNA7	CSPG5
GRIN2D	DRD4 11p15.5	HTR5A			GRP78
GRIN3A	DRD5 4p16.1	HTR6			HRH2
AMPA		HTR7			MC5R
GRIA3					OPRM1
GRIA4					TAAR6
GRID1					
Metabotropic					CSF2RA
GRM3					GFRA1
GRM4					RTN4R
GRM5					
GRM7					

Figure 6: A screen shot of the HSV-2 BLAST results using the filter "dopamine receptor". The repeated patterns correspond to dopamine receptors on different chromosomes as shown in Table 1. Homology with glutamate, serotonin, GABA, acetylcholine and other receptors is also noted.

its interactome, contain vatches that are homologous to proteins expressed by the Rubella virus (Figure 5). (Other viruses also display this property, although the interactome members targeted are distinct, and specific for each virus (see http://www) .polygenicpathways.co.uk/vatches.htm). Upon infection, viruses might therefore be considered as extraneous spurs to these types of protein/protein networks, and are likely to markedly affect their integrity. Indeed, several viruses, including herpes simplex, hepatitis C, Epstein-Barr, the cytomegalovirus, adenovirus and Coxsackie virus are known to bind to DISC1 interaction partners (Table 4).

3.4. Viral DNA within the Human Genome. The insertion of viral DNA into the human genome had until recently been thought to be the preserve of retroviruses. However the incorporation of DNA into mammalian genomes has recently been demonstrated on a large scale for both RNA and DNA viruses. Viral integration may be mediated by nonhomologous recombination with chromosomal DNA or, in the case of RNA viruses, by interactions with host chromosomal retrotransposons [68, 69]. It has also been shown the herpes virus HHV-6 can be transmitted from parent to child via chromosomal integration [70]. The

BLAST analyses of the viruses detailed in this paper, and of others at http://www.polygenicpathways.co.uk/blasts.htm clearly show that viral DNA from many species is present within the human genome. This viral homology may well cover the entire human genome. For example, a Blast of human chromosome 10 against all viral genomes (almost 3,000 viral forms) yielded 119,857 hits with entire coverage of 135.5 million bases. Viral DNA is thus both inter and intragenic (Figure 1). It has been proposed that retroviral integration, into paternal and maternal gene lines, inserting several genes at once and effectively creating a new being, is responsible for evolutionary saccades [71]. The fact that RNA and DNA nonretroviruses can also be so incorporated has important implications in this area.

The HSV-2 virus is homologous to several dopamine receptors and the BLAST pictogram shows how the same virus provokes repeating patterns in the human proteome (Figure 6). The same is true of the Herpes simplex virus (HSV-1) which is homologous to multiple lipoprotein receptors as well as to multiple kinases or of the cytomegalovirus which expresses proteins homologous to many chemokine receptors (see http://www.polygenicpathways.co.uk/blasts.htm). One interpretation of this, given the ability of chromosomal integration, is that repeated viral visits to the human genome over millions of years are responsible for the creation of gene families.

It is also possible that viral/human homology reflects convergent viral evolution, although this is difficult to reconcile with the presence of viral DNA in intergenic regions, for which there would be little evolutionary drive or selective pressure. It is also plausible that a bidirectional transfer of human and viral DNA could be at work.

For whatever reason, the result is that human proteins resemble those expressed by a multitude of today's viruses and other pathogens. Upon infection, these pathogens are thus able to interfere with the function of their human counterparts in a number of ways (see below).

3.5. Copy Number Variations and the Effects of Parental Age on Risk. Repeated viral insertion could well explain copy number variations, which are associated with a number of diseases, including schizophrenia [72, 73]. As their number increases, so will the number of matches to the same viral proteins, thus increasing the risk of viral interference and autoimmunity. As viral infection can be passed from parent to child via chromosomal integration, perhaps this is also why both paternal and maternal older age have been reported as risk factors in schizophrenia and other disorders [74, 75].

3.6. KEGG Pathway Analysis of Schizophrenia Susceptibility Genes. The color-coded pathways for this analysis are posted at http://www.polygenicpathways.co.uk/keggszgenes.htm. It confirmed the involvement of a number of polygenic pathways, including long-term potentiation and oxidative stress [3] growth factor/neuregulin pathways [121], neuroactive ligand pathways (dopamine/serotonin/glutamate and others) as well as dopamine metabolism pathways [9]. In the context of this review, a large number of immune-related pathways are traced out by these genes, together with many pathogen-related pathways, including toxoplasmosis, which heads the list (Table 5). The involvement of schizophrenia related genes in the life cycles of pathogens has been the subject of a previous review [22] and this relationship is supported by this analysis. Other pathogen related pathways relating to amoebiasis, Staphylococcus aureus and Helicobacter pylori infection, might indicate the involvement of other pathogens in schizophrenia, although such pathways could also be considered as generic pathways related to many pathogens.

There is no specific viral life cycle pathway within the KEGG dataset. However, viruses use adhesion molecules as receptors, endocytosis for cellular entry and the intracellular actin and tubulin networks for migration to and from the nucleus, mediated via dynein and kinesin motors. They also subjugate intracellular vesicular trafficking pathways, and are able to subvert both lysosomal and phagosomal pathways. Their exit may depend upon exocytosis, or by apoptotic or other means of killing their host cell [122]. These pathways are heavily represented within the schizophrenia gene analysis.

3.7. Mechanisms of Action. Individual proteins are homologous to multiple viral proteins, which nevertheless are specific for a spectrum of viruses, while individual viruses are homologous to a large but specific subset of human proteins.

Our proteomes therefore contain proteins with sequences exactly matching those in the current virome, and in the proteomes of bacteria and other pathogens, which are also subject to phage or viral infection. Pathogens' proteins are therefore homologous to receptors, transporters, peptide messengers, growth factors, and other protein products of diverse gene families. Upon infection, surrogate dopamine, NMDA serotonin and other receptors, as well as transporters and enzymes are made available, which in effect may steal the ligands of their human counterparts. It is already known that the dopaminergic ligand, amantadine, binds to the influenza virus [123], which expresses proteins homologous to dopamine receptors (Table 3). When homologous to peptide ligands, viral proteins may occupy and block or perhaps stimulate their cognate receptors, or use them for entry, as is the case with the AIDS virus and the CCR5 and CXCR4 chemokine receptors [124].

This is illustrated by the Norovirus (Norwalk) which causes vomiting sickness. The virus expresses proteins homologous to monoamine and other amine oxidases as well as to a number of dopamine and monoamine transporters (Table 6). Dopamine subversion by the viral homologues would be expected to increase dopamine levels resulting in emesis, thus explaining the recurrent vomiting produced by infection.

The potential interference by viruses within protein/ protein networks is well illustrated by the homology of rubella proteins to DISC1 and other members of its interactome, and by the fact that many viruses have indeed been found to bind to these components (Table 4).

The homologous human proteins of the viral risk factors implicated in schizophrenia correspond to the genomic

Table 1: Some of the pathogens implicated in Schizophrenia, either in relation to maternal infection, or to infection in later life.

Pre- and perinatal maternal infection	Juvenile (in offspring)	Adult
Rubella (first trimester) [76]: Influenza (first trimester) [13] Influenza or common cold with fever (second trimester) [16]	Mumps or cytomegalovirus infection (0–12 years old) [77]	HSV-1 seropositivity related to grey matter volume [78]
Poliovirus (second trimester) [17]	Coxsackie B5 infection perinatally [18]	HSV-1 (in Afro-Americans) or HHV-6 seropositivity: Inverse correlation with HSV-2 and cytomegalovirus [79]
Measles, Varicella zoster or polio (seropositivity at birth) [14]	Childhood meningitis (0–4 years old) [80]	Borna disease virus seropositivty [81]
HSV-2 (antibodies assayed at the end of pregnancy) [82]		Coronavirus seropositivity [83]
Influenza B (seropositivity at birth) [84]		Elevated retrovirus HERV-W transcripts [85]
Toxoplasmosis (antibodies during pregnancy) [86]		Measles virus seropositivity [87]
		Hepatitis C [38]
		Toxoplasmosis [88]
		Correlation with the incidence of Lyme disease (Borrelia) [20]

Table 2: Pathogens expressing proteins with homology to the autoantigens reported in schizophrenia. The size of the tags is proportional the number of pathogen's proteins that are homologous to the autoantigen. Note that the profile is different for each pathogen. The original BLAST files can be found at http://www.polygenicpathways.co.uk/blasts.htm.

Autoantigen reference	Pathogens
CHRNA7 Nicotinic cholinergic receptor [89]	Rubella Rhinovirus T. Gondii Varicella Borrelia Herpesvirus 2
CHRM1 Muscarinic cholinergic receptor [90]	Herpesvirus 2 Varicella Borrelia Influenza T.Gondii Rhinovirus Rubella
DRD2 Dopamine receptor [82]	Varicella Herpesvirus 2 Influenza Rubella Rhinovirus T. Gondii
GRIN1 NMDA receptor subunit [91]	T. Gondii Herpesvirus 2 Influenza Varicella Borrelia Rubella Rhinovirus
ELANE Leukocyte elastase [92]	T. Gondii Rhinovirus Borrelia Influenza Rubella Varicella
OPRM1 Opioid receptor [93]	Varicella Rubella Borrelia Herpesvirus 2 Influenza T. Gondii Rhinovirus
NGF Nerve growth factor [92]	Rhinovirus Borrelia Herpesvirus 2 Varicella Rubella T. Gondii Influenza
HTR1A Serotonin receptor [93]	Rubella Rhinovirus Varicella T. Gondii Influenza Herpesvirus 2 Borrelia
HSP60 Heat shock protein 60 [94]	Influenza Herpesvirus 2 T.Gondii Rubella Borrelia Varicella
HSPA12A Heat shock protein 70 [95]	Influenza T. Gondii Varicella Rubella Herpesvirus 2 Borrelia
HSP90 Heat shock protein 90 [95]	Rhinovirus Influenza Herpesvirus 2 Rubella Varicella T. Gondii
PAM/MYC [94]	Herpesvirus 2 Rubella Borrelia T. Gondii Influenza Rhinovirus
S100B [96]	Borrelia Influenza Rubella Rhinovirus Varicella Herpesvirus 2
STRN Striatin [96]	Rubella Rhinovirus T. Gondii Influenza Borrelia Herpesvirus 2 Varicella

locations of 632 schizophrenia susceptibility genes (see Venn diagrams). Both negative and positive genetic association results have been reported for these many genes and it now seems plausible that, in some cases, this may be due to the presence or absence of active infection with these and other pathogens, and that DNA assays have been detecting pathogen as well as human DNA in the blood samples used for assay. There is evidently no way of discriminating viral or bacterial double-stranded DNA from human DNA.

This is not specific to schizophrenia, as the viruses implicated in Alzheimer's disease (HSV-1, HIV-1, HHV-6 and the cytomegalovirus) [125–127] are also homologous to proteins encoded by Alzheimer's disease susceptibility genes see http://www.polygenicpathways.co.uk/blasts.htm [128].

It seems that a viable interpretation, given the same phenomenon in these diseases, is that these genes are susceptibility genes precisely because they encode for proteins with homology to the viral risk factors. Infection and genetics

Table 3: Human proteins with homology to proteins expressed by pathogens. The size of the tags reflects the number of pathogen's proteins that are homologous to the human protein: the filters used are described. The number of schizophrenia susceptibility genes within each of these datasets is shown in the left-hand column. Certain genes are classified according to family and are highlighted in red. Gene definitions and the original BLAST files can be found at http://www.polygenicpathways.co.uk/blasts.htm. Note that the homologues are often clustered in families (e.g., HTR1A, HTR2A, HTR3A, HTR3B, HTR3E, HTR5A, and HTR7).

Pathogen	Human protein Homologues
HERV-W Filter "schizophrenia" Number of SZ genes = 103 ABCA13 ACSM1 AHI1 ALDH1A2 ANK3 ARHGAP18 ARHGEF10 ARVCF ASTN1 BRD1 CACNG2 CHRFAM7A CIT CLINT1 COMT CPLX2 CSF2RB CSPG5 CTNND2 DAO DGKI DISC1 DRD2 DRD3 DRD5 DTNBP1 EGR4 FEZ1 GABBR1 GFRA1 GFRA3 GNPAT GPC1 GPR85 GRIA3 GRIA4 GRID1 GRIK3 GRIN2A GRIN2D GRM3 GRM4 GRM7 HDAC4 HIPK3 HIST1H2AG HIST1H2AH HLA-DRB1 HOMER1 HOMER2 HTR1A HTR2A HTR5A HTR7 IMPA2 JARID2 KCNH2 LIF MAP6 MAPT MCHR1 MCTP2 MDGA1 MEGF10 MLC1 MOG MPZL1 MUTED NALCN NDUFV2 NEUROG1 NOS1 NOTCH4 NRG1 NRG3 NRXN1 NTNG2 PCM1 PCNT PDE4B PDE7B PI4KA PIK3C2G PLXNA2 PPP3CC PRSS16 QK1 RAPGEF6 RELN RPGRIP1L RSRC1 SLC18A2 SP4 SPRY4 ST8SIA2 SULT4A1 SYN2 SYN3 TAAR6 TH YWHAH ZNF184 ZNF804A	Dopamine related ALDH1A2 COMT DDC DRD2 DRD5 SLC18A2 TH Serotonin related HTR1A HTR2A HTR3A HTR3B HTR3E HTR5A HTR7 Glutamate related DAO GRIA2 GRIA3 GRIA4 GRID1 GRIN2A GRIN2D GRIN3A GRIK3 GRIK5 GRM2 GRM3 GRM7 Synaptic CABIN1 CPLX2 DTNBP1 DRP2 GRIP1 RPGRIP1L HOMER1 HOMER2 HOMER3 HIPK3 SPTAN1 SYN2 SYN3 RGS9 SNX6 GABA related GABRB1 GABRG1 GABBR1 Cholinergic CHRFAM7A DISC1 related ATF7IP DISC1 FEZ1 MLC1 PCM1 PCNT Myelin related MBP MOG MPZL1 NOTCH4 Translation initiation EIF3D EIF4A2 Neuregulin and growth EGR4 GFRA1 CSF2RB GFRA3 NRXN1 NLGN4X RET UTRN Oxidative stress NDUFV2 ATP2A2 CBR1 NDUFS1 Channels Calcium CACNA1B CACNG2 Sodium NALCN Potassium KCNH2 KCNH7 KCNH6 KCNN2 Immune/cytokine LIF TPI1 Structural MAP1A MAPT MYO1D MAP1B TBCB TUBB2A Signalling DGKI GNB1 IMMT PDE10A PIK3C2G PI4KA PAK3 PPP3CC GNAI2 RAPGEF6 RASF7 STK24 DiGeorge DGCR14 ABCA7 ADAM28 AHI1 ANK2 ANK3 ANKHD1 APOL4 APP

Table 3: Continued.

	AP3B2 ASTN1 BACE1 BRPF3 BRD1 CARTPT CEP63 CLDN10 CLINT1 CTNND2 CYFIP1 CYP26B1 DCDC2 DKK1 DLD DNAJC6 DOCK9 DZIP1 FNIP1 GDA GNPAT GPC1 GPR125 HDAC4 HDAC10 HNTPNU HIST1H2AH HSPD1 JARID2 KIF13A LAMB2 LANCL2 LSAMP MCHR1MDGA1 MCTP2 MTIF3 MUTED NC5C NBEAL2 PAFAH1B1 PAICS PCDHA1 PCDH11Y PLXNA2 PNP0 PRSS16 PTGFRN RAI1 RSRC1 SEL1L3SEMA3A SIGMAR1 SIRPB1 SLC25A3(PO_4) SLCO3A1(anion) SP4 STAB1 ST6GAL2 STRN SULT4A1 TAAR6 TKT TMTC4 TPM1 UCHL1 UGGT2 WDR1 ACSM1 SPRY4 ST8SIA2 YWHAH ZBT20 ZNF184 ZNF804A OMG VGF MEGF10 ERVWE1 HIST1H2AG TMEM200C OLFM1 ABCA13 ARVCF CCDC141 EPHA6 PRKCG ADAMTS4 ARHGAP18 NRCAM NOVA1 COX1 DRD3 GPR85 GRIK1 KCNQ5 CNTN4 GNB2 OPHN1 RELN HNRNPA2B1 INA ALDH1A3 VAMP2 KIF21A UBAC2 CSPG5
HSV-2 Filter "schizophrenia" Number of SZ genes = 166 ABCA13 ACSL6 ADAM12 ADCYAP1 ADSS AHI1 ALDH1A2 ALDH3B1 ALK ANK3 ARHGAP18 ARVCF ASTN1 ASTN2 ATP6 BRD1	Dopamine related COMT DDC DRD1 DRD3 DRD4 DRD5 TH PEMT Serotonin related HTR2A HTR6 HTR7 HTR5A Glutamate related DAO DAOA GRIA4 SLC1A4(GLUT) GRID1 GRIN2D GRIN3A GRM3 GRM4 PRODH SLC17A1SLC17A7(PO4/glu) SLC1A3(GLUT) KMO GABA – related GABRA1 GABBR1 Synaptic DLG4 DTNBP1 HOMER1 HOMER2 NOS1AP SYN2 SYNGAP1SYT11 RGS4 DISC1 related DISC1 CIT FEZ1 FZD3 NDE1 NDEL1 PDE4B TSNAX Neuregulin and growth ALK EGR2

Table 3: Continued.

BTN3A1 CACNA1C CCDC60 CCKAR CDKN2A CHN2 CHRM5 CHRNA7 CIT COMT CSF2RA CSF2RB CSPG5 CYTB DAO DAOA DBH DGCR2 DGCR6 DISC1 DKK4 DLG4 DLX1 DRD2 DRD3 DRD4 DRD5 DTNBP1 EGR2 ENO2 FABP7 FEZ1 FGF14 FXR1 FZD3 GABBR1 GABRA1 GABRP GCLM GFRA1 GNAL GNB1L GNL3 GRIA3 GRIA4 GRID1 GRIN2A GRIN2D GRM3 GRM4 GRM5 GRM7 HIST1H2AG HIST1H2AH HOMER1 HOMER2 HSPA12A HTR1A HTR2A HTR2C HTR5A HTR6 HTR7 IL1A IMPA2 JARID2 KCNH2 KCNN3 KMO MAG MAP4 MAP6 MAPK14 MC5R MCTP2 MDGA1 MEGF10 MICB MLC1 MPZL1 MUTED MYH9 MYT1L ND2 NDE1 NDEL1 NDUFV2 NEUROG1 NOS1AP NOTCH4 NPAS3 NPTN NRG1 NRG3 NRXN1 NTF3 NUMBL OPRM1 PADI2 PCM1 PDE4B PDE4D PDLIM5 PEMT PLA2G4C PLAA PLXNA2 PNPO POM121L2 PPP1R1B PPP3CC PRODH PRSS16 PTBP2 RAPGEF6 RELN RGS4 RPGRIP1L RTN4R SHISA5 SIRT5	GFRA1 NRG1 NRG3 NRXN1 NTF3 NPTN FGF14 CSF2RB NTNG Myelin related MAG MPZL1 NOTCH4 RTN4R Oxidative stress GCLM ATP6 ND2 Channels Calcium CACNA1C Potassium KCNN3 KCNH2 Immune/cytokine IL1A MICB TRAF3IP1 Structural MAP4 MAP6 MYH9 MYT1L Signalling ARHGAP18 ARHFGEF10 GNAL MAPK14 IMPA2 PDE4D PLAA PLA2G4C PPP1R1B RAPGEF6 UHMK1 DiGeorge DGCR2 DGCR6 ABCA13 ADAM12 ADSS AHI1 ARVCF BRD1 BT2NA2 CHN2 CSPG5 DLX1 ENO2 FBCL21FCYD6 GRP78 JARID2 KPNA3NPAS3 NUMBL OPRM1 PCDH8 PLXNA2 PNPO POM121L2 PRSS16 GRIN2A ALDH1A2 PCM1 TAAR6 VRK2 TXNDC5 1 GNL3 HTR2C NDUFV2 FXR1 MC5R DBH CDKN2A NEUROG1 PADI2 CCKAR MLC1 FABP7 ASTN2 CHRNA7 PPP3CC TUBA8 PTBP2 GRM7 TSPAN8 TPH1 HSPA12A SYN3 DKK4 CYTB CCDC60 PDLIM5 HIST1H2AH SLC06A1(ANION) MEGF10 RPGRIP1L MCTP2 MDGA1 GRIA3 YWHAE GNB1L SHISA5 ACSL6 GRM5 ZNF74 SMARCC1 BTN3A1 ASTN1 TSPO SLC17A3 DISC1 SYNGR1 CSF2RA SLC6A5(GLY) UFD1L ZNF804A CHRM5 YWHAZ MUTED SIRT5 HRH2 SPARCL1 HTR1A CABIN1 HIST1H2BJ
Influenza Filter "schizophrenia" Number of SZ genes = 167 ABCA13	Dopamine related COMT DRD1 DRD3 DRD5 Serotonin related HTR1A HTR2C HTR5A HTR6 HTR7 TPH1 Glutamate related DAO DAOA GRIA3 GRIA4 GRIN2A GRIN2D GRIN3A GRM5 KMO SRR SLC6A5(GLY) SLC17A7(PO4) SLC17A1 SLC17A3 GABA –related GABRA1 GABBR1 GABRP Synaptic DTNBP1 DLG4 HOMER1 RPGRIP1L SYN2 SYN3

Table 3: Continued.

ACSL6 ADAM12 ADCYAP1
ADSS AHI1 ALDH1A2
ALDH3B1 ALK ANK3
ARHGAP18 ARVCF ASTN1
ASTN2 ATP6 BRD1 BTN3A1
CCDC60 CCKAR CDKN2A
CHN2 CHRM5 CHRNA7 CIT
COMT CSF2RA CSF2RB
CSPG5 CYTB DAO DAOA
DBH DGCR2 DGCR6 DISC1
DKK4 DLG4 DLX1 DRD2
DRD3 DRD4 DRD5 DTNBP1
EGR2 ENO2 FABP7 FEZ1
FGF14 FXR1 FZD3 GABBR1
GABRA1 GABRP GCLM
GFRA1 GNAL GNB1L GNL3
GRIA3 GRIA4 GRID1 GRIN2A
GRIN2D GRM3 GRM4 GRM5
GRM7 HIST1H2AG
HIST1H2AH HIST1H2BJ
HOMER1 HOMER2 HSPA12A
HTR1A HTR2A HTR2C HTR5A
HTR6 HTR7 IL1A IMPA2
JARID2 KCNH2 KCNN3 KMO
MAG MAP4 MAP6 MAPK14
MC5R MCTP2 MDGA1
MEGF10 MICB MLC1 MPZL1
MUTED MYH9 MYT1L ND2
NDE1 NDEL1 NDUFV2
NEUROG1 NOS1AP NOTCH4
NPAS3 NPTN NRG1 NRG3
NRXN1 NTF3 NTNG1 NUMBL
OPRM1 PADI2 PCM1 PDE4B
PDE4D PDLIM5 PEMT
PLA2G4C PLAA PLXNA2
PNPO POM121L2 PPP1R1B
PPP3CC PRODH PRSS16
PTBP2 RAPGEF6 RELN RGS4
RPGRIP1L RTN4R SHISA5
SIRT5 SLC17A1 SLC17A3
SLC17A7 SLC1A3 SLC1A4
SLC6A5 SMARCC1 SNAP29
SP4 SPARCL1 SRR SYN2
SYN3 SYNGR1 SYT11 TH
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TSPAN8 TUBA8 TXNDC5
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ZNF804A

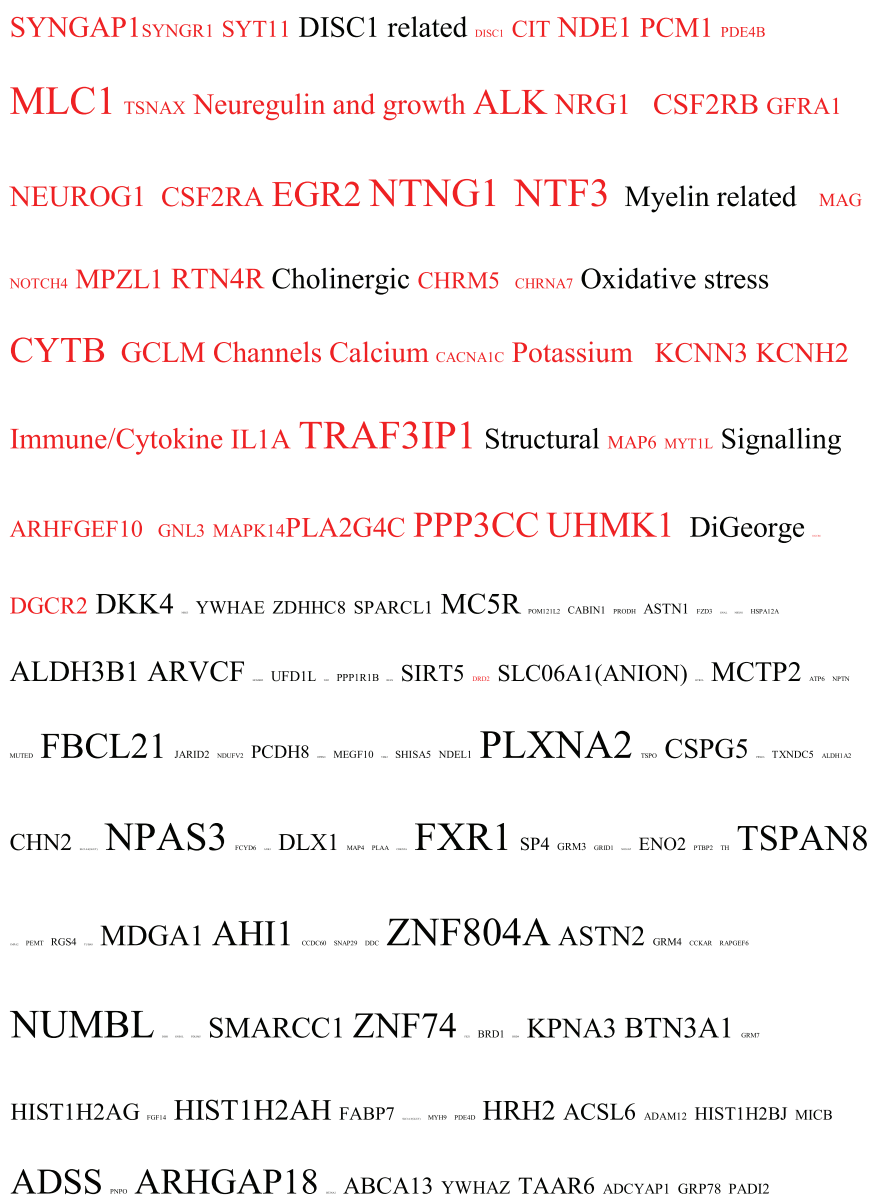


Table 3: Continued.

Rhinovirus Filter “schizophrenia” Number of SZ genes = 176	ABCA13 ACSL6 ADAM12 ADCYAP1 ADSS AHI1 ALDH3B1 ANK3 ANKK1 APOL2 ARHGAP18 ARHGEF10 ARVCF ASTN1 ASTN2 BRD1 BTN3A1 C10orf120 CACNA1C CCKAR CHI3L1 CHL1 CHRFAM7A CHRM5 CHRNA7 CIT CLDN5 CLINT1 CLOCK CNP COMT CSF2RA CSF2RB CTLA4 CTNND2 DAO DAOA DBH DGCR2 DGCR5 DGCR6 DGKI DISC1 DKK4 DLX1 DPYSL2 DRD2 DRD3 DRD4 DRD5 EGR4 ENO2 ESR1 FABP7 FEZ1 FGF14 FXR1 FZD3 GABBR1 GABRA1 GABRB2 GABRP GFRA3 GNB1L GNL3 GNPAT GRIA1 GRIA3 GRIA4 GRIK3 GRIN1 GRIN2A GRIN2D GRM3 GRM4 GRM5 GRM7 HIST1H2BJ HLA-DRB1 HOMER1 HOMER2 HSPA12A HTR1A HTR2A HTR2C HTR6 HTR7 IL1A IMPA2 INTS6 ITIH3 JARID2 KCNH2 KPNA3 LIF MAG MAP4 MAP6 MAPK14 MC5R MCHR1 MCHR2 MCTP2 MDGA1 MICB MLC1 MUTED MYH9 MYT1L ND2 ND4 NDEL1 NDUFV2 NOS1 NOS1AP NOTCH4 NPAS3 NPTN NRG1 NRG3 NRXN1 NTF3 NUMBL OPCML OPRM1 PADI2 PCM1 PCQAP PDE4B PDE7B PDLIM5 PFN4 PLA2G4C PLAA PNPLA8	Dopamine related DBH COMT DRD1 DRD2 DRD3 DRD5 TH SLC18A2 Serotonin related HTR1A HTR2C HTR6 HTR7 TDO2 Glutamate related DAO DAOA GRIN1 GRIN2A GRIK3 GRM4 GRM5 GRM7 SLC1A3(GLUT) SLC1A4(GLUT) SLC17A3 SLC17A7(PO4/glut) GABA – related GABRA1 GABRB2 GABBR1 Synaptic HOMER1 HOMER2 RPGRIP1L NOS1 NOS1AP SYNGR1 SYT11 RGS4 DISC1 related DISC2 CIT FEZ1 NDEL1 PDE4B PCM1 MLC1 Neuregulin and growth NRG1 NRG3 NPTN CSF2RA EGR4 FGF14 GFRA3 NRXN1 NTF3 Myelin related MAG NOTCH4 Cholinergic CHRNA7 CHRFAM7A Oxidative stress ALDH3B1 ND2 ND4 NDUFV2 Channels Calcium CACNA1B CACNA1C Potassium KCNH2 Immune /Cytokine LIF Structural MAP4 MAP6 signalling ARHGEF10 GNL3 ARHGAP18 IMPA2 PDE7B PK3C2G PPP1R1B RAPGEF6 UHMK1 PLAA PNPLA8 PLA2G4C VRK2 DiGeorge DGCR2 DGCR5 DGCR6 ABCA13 ITIH3 JARID2 FXR1 PADI2 GNB1L ORC3L SIL1 ZNF804A RELN DKK4 ADCYAP1 POM121L2 ADSS HSPA12A PPP3CC MYH9 INTS6 SP4 ESR1 PB1 TMEM108 PFN4 CHL1 AK1 CLOCK PNPO SPARCL1 OPCML ZDHC8 NUMBL SYN3 PTBP2 TSPAN8 ST8S1A2 ASTN1 HIST1H2BJ NPAS3 MCTP2 APOL2 TXNDC5 SGCR6 CTNND2 C10orf120 ANK3 HRH2 CLINT1 PRSS16 HTR2A MRCL3 MRLC2 DLX1 GLRA2 MICB PCQAP CLDN5 CHI3L1 BRD1 DPYSL2 ENO2 GNPAT SULT4A1 ABCA1 MCHR1 TAAR6

Table 3: Continued.

PNPO POM121L2 PPP1R1B PPP3CC PRODH PRSS16 PTBP2 RAPGEF6 RELN RGS4 RPGRIP1L SHISA5 SIL1 SIRT5 SLC17A3 SLC17A7 SLC18A2 SLC1A3 SLC1A4 SLC1A6 SLC6A5 SMARCC1 SP4 SPARCL1 SULT4A1 SYN2 SYN3 SYNGR1 SYT11 TAAR6 TDO2 TH TMEM108 TSPAN8 TXNDC5 UHMK1 VRK2 ZBED4 ZNF184 ZNF804A	BTN3A1 ANKK1 MACF1 SHISA5 MDGA1 PRODH ZBED4 CTLA4 ZNF184 SIRT5
Rubella Filter "schizophrenia" Number of SZ genes = 179 ADAM12 ADCYAP1 ADSS AHI1 ALDH1A2 ALDH3B1 ANK3 ARHGAP18 ARHGEF10 ARVCF ASTN1 ASTN2 ATP6 BDNF BRD1 BTN2A2 CACNA1C CCDC60 CCKAR CDKN2A CHN2 CHRM5 CHRNA7 CLOCK COMT CSF2RA CSF2RB CSPG5 CYTB DAO DAOA DBH DGCR2 DGCR6 DISC1 DKK4 DRD2 DRD3 DRD4 DRD5 DTNBP1 EGR2 ENO2 ERBB2 ERBB3 ERBB4 FABP7 FBXL21 FEZ1 FGF14 FXR1 FXYD6 FZD3 GABBR1 GABRA1 GABRB2 GABRP GCLM GFRA1 GNAL GNB1L GNL3 GPC1 GRIA3 GRIA4 GRID1 GRIK3 GRIN1 GRIN2A GRIN2D GRM3 GRM4 GRM5 GRM7 HIST1H2AG HIST1H2AH HIST1H2BJ HLA-DRB1 HOMER1 HOMER2 HTR1A HTR2A HTR2C HTR5A	Dopamine related COMT DBH DRD3 DRD4 DRD5 PEMT Serotonin related HTR1A HTR2A HTR2C HTR5A HTR7 TPH1 Glutamate related DAO DAOA GRIA3 GRIA4 GRID1 GRIN1 GRIN2A GRM3 GRM4 GRM5 GRM7 KMO SLC1A4(GLUT) SLC17A3 GABA – related GABRA1 GABBR1 GABRB2 GABRP Cholinergic CHRM5 Synaptic CABIN1 DTNBP1 NOS1AP RPGRIP1L SNAP29 SYN2 SYN3 RGS4 SYNGAP1SYNGR1 SYT11 DISC1 related DISC1 PCM1 PDE4B NDEL1 FEZ1 FZD3 Neuregulin and growth NRG1 ERBB1 ERBB3 ERBB4 GFRA1 NTF3 NTNG1 FGF14 Myelin related NOTCH4 RTN4R QK1 Oxidative stress CYTB GCLM ND2 NDUFV2 Channels Calcium Potassium KCNN3 KPNA3Immune/cytokine IL1A TRAF3IP1Structural MAP6 MYT1L Signalling ADCYAP1AK1 ARHGEF10 CDKN2A GNAL GNB1L GNL3 MAPK14 IMPA2 PLAA PLA3G4C REPGEF6 PDE4D PPP1R1B DiGeorge DGCR2 DGCR6 ERBB2 MEGF10 NDE1 HIST1H2AG A12A TXNDC5 ASCL6 SHISA5 ZNF804A JARID2 FXYD6 BTN2A2 FBXL21 NRXN1 CHRNA7 NUMBL ARVCF HTR6 ALDH1A2 SPARCL1

Table 3: Continued.

HTR6 HTR7 IL1A IMPA2 JARID2 KCNH2 KCNN3 KMO KPNA3 KREMEN1 MAG MAP4 MAP6 MAPK14 MC5R MCTP2 MDGA1 MEGF10 MICB MLC1 MPZL1 MUTED MYH9 MYT1L ND2 NDE1 NDEL1 NDUFV2 NEUROG1 NOS1 NOS1AP NOTCH4 NPAS3 NPTN NRG1 NRG3 NRGN NRXN1 NTF3 NTNG1 NTNG2 NUMBL OPRM1 PADI2 PCM1 PDE4B PDE4D PDLIM5 PEMT PLAA PLXNA2 POM121L2 PPP1R1B PPP3CC PRODH PRSS16 PTBP2 QK1 RELN RGS4 RPGRIP1L RTN4 RTN4R SHISA5 SIRT5 SLC17A1 SLC17A3 SLC18A2 SLC1A3 SLC1A4 SLC6A5 SLCO6A1 SMARCC1 SNAP29 SP4 SPARCL1 SRR SYN2 SYN3 SYNGR1 SYT11 TAAR6 TH TRAF3IP1 TSNAX TSPAN8 TUBA8 TXNDC5 UFD1L UHMK1 VRK2 YWHAE ZDHHC8 ZNF74 ZNF804A	TSPO CCDC60 YWHAE KCNH2 DRD1 MLC1 CSPG5 PLXNA2 MCTP2 GPC1 VRK2 CCKAR ASTN2 SLC1A3(GLUT) PPP3CC FXR1 ASTN1 GRIN2D MICB PTBP2 SRR NRG3 EGR2 MPZL1 CSF2RB SMARCC1 BDNF TH HRH2 ADAM12 PCDH8 MAG ZNF74 YWHAZ ATP6 CHN2 ANK3 TSPAN8 PER1 TUBA8 ARHGAP18 NRGN MYH9 ENO2 SIRT5 BRD1 HOMER2 GRP78 TAAR6 HIST1H2BJ KREMEN1 SLCO6A1 HIST1H2AH CLOCK PRSS16 PADI2 PDLIM5 MDGA1 CACNA1C ADSS ZDHHC8 AHI1 OPRM1 UFD1L NPAS3 MC5R POM121L2 DKK4
Varicella Filter “schizophrenia” Number of SZ genes = 75	Dopamine related COMT DDC DRD2 DRD5 Serotonin related HTR2C HTR7 HTR3A HTR3D TPH2 TPH1 Glutamate related GRIN1 GRIN3A GRIN2A GRIK1 GRIK5 GRM2 GRM7 SLC6A5(Gly) SLC17A6 GABA –related GABRA5 GABBR1 Synaptic DLGAP2 RPGRIP1L NOS1AP RGS9 SPTBN4 HIPK3 STX7 SYNGR1 DISC1 related DISC1 CIT FEZ1 PCNT PCM1 PDE4B Neuregulin and growth NRG1 NRG3 NTF3 NTNG2 CSF2RA NRXN1 EGR2 NRXN3 NLGN4X UTRN VGF Myelin related NOTCH1 OMG Cholinergic CHRM5 CHRFAM7A Oxidative stress COX2 ND1 ND5 NDUFS1 QDPR Channels
ABCA13 ACSL6 ALDH1A2 ANK3 ANKK1 ARHGAP18 ASTN1 BRD1 BTN3A2 CACNA1C CHRFAM7A CHRM5 CHRNA7 CNTNAP2 COMT CSPG5 CTNND2 CTXN3 DAO DBH DGCR2 DGKI DPYSL2 DRD2 DRD5 ESR1 FZD3 GABBR1 GABRA1	

Table 3: Continued.

	GNPAT GRIK3 GRIN1 GRIN2A GRIN2D GRM5 GRM7 HDAC3 HDAC4 HIPK3 HLA-DRB1 HTR2C HTR7 KCNH2 KREMEN1 MAP6 MAPK14 MCHR1 MCTP2 MICB MYT1L NALCN NEUROG1 NOS1 NOS1AP NPAS3 PDE7B PI4KA PLAA PLXNA2 PTBP2 RAPGEF6 RPGRIP1L SEMA3D SLC17A6 SLC6A5 SLC6A1 SP4 SPARCL1 SULT4A1 TAAR6 TPH1 TRMT2A UHMK1 VRK2 ZNF804A
T.Gondii Filter "schizophrenia" related	Calcium CACNA1C Potassium KCNH7 KCNQ5 KCNH2 Immune/cytokine IL1RAPL1 LIFR Structural NEFM MAP1A MAP1B MAP6 MYHP MYT1L Signalling CDC42 GNB1 DAG1 DGKI UHMK1 GUCY1A2 PI4KA PLAA PRKCG PDE10A RAPGEF6 GSK3A RASSF7 VRK2 DiGeorge DGCR2 DGCR14 MACF1 NR3C1 ESR1 CTNND2 APP SE2 GPM6A INA STAB1 PCDHB11 FIGN CPNE2 AP3B2 SULT4A1 CELF4 MICB MCHR1 CNTNAP2 AP3D1 MCF2 YWAH ANKHD1 PCDH11Y PSMD10 GABRD SLC6A2(NE) ORC3L PTBP2 ZNF804A CSPG5 NUDT6 HDAC4 NCOA7 CHRNA7 PCDH8 AP3M1 TRMT2A TRIM3 ZBER4 RNH1 ANKK1 MBLN2 SEMA3B SLC26A6 PLXNA2 ENTPD4 LAMB2 HP1BP3 TPM3 ADAMTS4 DPYSL2 GPR109B CLDN10 NPAS1 BRD1 CTXN3 HRH2 BACE1 ASTN1 ARHGAP18 (GLY) DNAJC6 AADAT ALDH1A2(retinoic) ITIH4 DBP GNPAT ATP2B2 DOCK9 APOL3 SPARCL1 KIF13A MECP2 SIRPB1 MAGEL2 TAAR6 EPHA6 ATP6V1A NRCAM USP4 LMNB2 CAMKV MCTP2 PCDHA1 UGGT2 PADI2 FNIP1 KIF21A EPB41L1 ARNTL2 ACLY ANK3 KIAA0513 ABCA13 SORBS1 PTGFRN SEMA3D RET RAI1 SLCO6A1 SLC25A3 SP4 LANCL2 SRSF6 CACNA1B SETD2 HDAC3 GABRA1 ATP5A1
Filter	Dopamine related COMT DBH DRD5 DRD3 DRD4 PEMT SLC18A2 TH Serotonin related HTR1A HTR2A HTR2C HTR5A TPH1 Glutamate related DAOA GRIA4 GRIN1 GRIN2A GRIN2C GRIN2D GRIK3

Table 3: Continued.

SZ genes = 182 ADAM12 ADCYAP1 ADSS AHI1 ALDH1A2 ALDH3B1 ANK3 ARHGAP18 ARHGEF10 ARVCF ASTN1 ASTN2 ATP6 BRD1 BTN2A2 BTN3A1 CACNA1C CCDC60 CCKAR CDKN2A CHN2 CHRM5 CHRNA7 CLOCK COMT CSF2RA CSF2RB CSPG5 CYTB DAO DAOA DBH DGCR2 DGCR6 DISC1 DKK4 DLX1 DRD2 DRD3 DRD4 DRD5 DTNBP1 EGR2 ENO2 ERBB2 ERBB3 ERBB4 FABP7 FBXL21 FEZ1 FGF14 FXR1 FXYD6 FZD3 GABBR1 GABRA1 GABRB2 GABRP GCLM GFRA1 GNAL GNB1L GNL3 GRIA3 GRIA4 GRID1 GRIK3 GRIN1 GRIN2A GRIN2B GRIN2D GRM3 GRM4 GRM5 GRM7 HIST1H2AG HIST1H2AH HIST1H2BJ HLA-DRB1 HOMER1 HOMER2 HSPA12A HTR1A HTR2A HTR2C HTR5A HTR6 HTR7 IL1A IMPA2 JARID2 KCNH2 KCNN3 KMO KPNA3 KREMEN1 MAG MAP4 MAP6 MAPK14 MC5R MCTP2 MDGA1 MEGF10 MICB MLC1 MPZL1 MUTED MYH9 MYT1L ND2 NDE1 NDEL1 NDUFV2 NEUROG1 NOS1 NOS1 NOS1AP NOTCH4 NPAS3 NPTN NRG1 NRG3 NRXN1 NTF3 NTNG1 NTNG2 NUMBL OPRM1 PADI2 PCM1 PDE4B PDE4D PDLIM5 PEMT PLA2G4C PLAA PLXNA2 PNPO POM121L2 PPP1R1B PPP3CC PRODH PRSS16 PTBP2 QK1 RAPGEF6 RELN RGS4 SHISA5 SIRT5 SLC17A1 SLC17A3 SLC17A7 SLC18A2 SLC1A3 SLC6A5 SLCO6A1	GRM3 GRM4 PRODH KMO SLC6A5(GLY) SLC17A1 GABA –related GABRP Synaptic DTNBP1 CABIN1 HOMER1 NOS1NOS1AP SYNGAP1 SYN2 SYN3 SNAP29 SYNGR1 SYT11RGS4 DISC1 related DISC1 FEZ1 FZD3 NDE1PDE4B TSNAX MLC1 Neuregulin and growth ERBB2 ERBB3 EGR2 FGF14 GFRA1 NEUROG1 NTF3 NRXN1 NTNG2Myelin related MAG MPZL1 QK1 Cholinergic CHRNA7 Oxidative stress ATP6 GCLM ND2 NDUFV2 Immune/cytokine IL1A MICB TRAF3IP1 Signalling ADCYAP1 ARHGEF10 CDKN2A GNAL GNL3 ARHGAP18 MAPK14 GNB1L PLA2G4C PLAA PPP3CC PPP1R1B RAPGEF6 UHMK1 VRK2 Structural MAP4 MYT1LMYH9 TUBA8 DiGeorge DGCR2 DGCR6 Circadian CLOCK PER1 AHI1 AK1 ALDH3B1 ANK3 ARVCF ASTN2 BRD1 BTN2A2 BTN3A1 CCDC60 CCKAR CHN2 CSPG5 DKK4 ENO2 FABP7 FXYD6 GRP78 HIST1H2AH HIST1H2AG HIST1H2BJ KPNA3 KREMEN1 PDLIM5 SLC1A3(GLUT) MDGA1 MC5R MCTP2 DRD2 CHRM5 NPAS3 PNPO PTBP2 RELN SHISA5 SIRT5 TAAR6 TSPAN8 TXNDC5 YWHAE YWHAZ ZDHHC8 ZNF74 CSF2RB DRD1 SRR GRID1 GABRA1 SP4 SPARCL1 ZNF804A TSPO JARID2 HTR6 HOMER2 ALDH1A2 PDE4D MEGF10 SLCO6A1 NOTCH4 DLX1 ASCL6 PRSS16 UFD1L GRIA3 OPRM1 HRH2 KCNH2 CYTB CSF2RA NRG1 PLXNA2 NDEL1 FXR1 IMPA2 GRM5 SMARCC1 NPTN NRG3 GABRB2 NTNG1 PCDH8 SLC17A3 GRM7 SLC17A7(PO4) DAO

Table 3: Continued.

SMARCC1 SNAP29 SP4 SPARCL1 SRR SYN2 SYN3 SYNGR1 SYT11 TAAR6 TH TPH1 TRAF3IP1 TSNAX TSPAN8 TUBA8 TXNDC5 UFD1L UHMK1 VRK2 YWHAE ZDHHC8 ZNF74 ZNF804A	
Borrelia Burgdorferri Number of SZ genes = 167	**Dopamine** ALDH1A2 DRD2 DRD3 DRD4 DRD5 MAOB **Serotonin** HTR1A HTR3C HTR6 HTR3D HTR3E SLC6A5 TDO2 **Glutamate** DAOA GLUL GRIA3 GRIA4 GRIN1 GRIK1 GRIK3 GRIK5 GRIN2A GRM2 GRM3 GRM4 PRODH SLC1A3 SLC1A5 SLC1A4 GABA GABBR1 GABRB2 GAD1 GAD2 **Cholinergic** CHRM5 **synaptic** BLOC1S1 CABIN1 CNTN4 CPLX2 DLG1 GPRASP2GRIP1 HOMER2 HOMER3 RGS4 RGS9 SHANK3 SNAP29 SPTAN1 SYNGAP1 STXBP1 SYNGR1 SYN2 SYN3 SYT5 **DISC1 related** DISC1 FEZ1 IMMT MLC1 NDE1 NDEL1 PCM1 PCNT PDE4B TSNAX **Neuregulin/ growth** EGR4 EGR2ERBB4 FGF14 NRG1 NRG3 **Immune** IL1RAPL1 LIFR TPI1 **Signalling** CSNK1D GSK3A IMPA2 PIP4K2A PLA2G4C PLA2G4D SH3GL2 STK24 **Channels** CACNA1B CACNG2 KCNH5 KCNH6 KCNN2 KCNQ5 **Myelin** CNP MOBP OMG RTN4R Structural ACTB ACTG1
ABCA13 ACSL6 ADCYAP1 ADSS AGBL1 AHI1 AKT1 ALDH1A2 ALDH3B1 ANK3 ANKK1 APOL2 ARHGAP18 ARHGEF10 ASTN1 ASTN2 BRD1 CACNG2 CCDC60 CCKAR CHL1 CHN2 CHRM5 CHRNA7 CIT CLINT1 CLU CNP CNTNAP2 CPLX2 CSF2RA CSPG5 CTNND2 DAOA DBH DGCR2 DGKI DISC1 DLG1 DPYSL2 DRD2 DRD3 DRD4 DRD5 DYM EFNB2 EGR2 EGR4 ENO2 ERBB4 FBXL21 FEZ1 FGF14 FOXP2 FXR1 FZD3 GABBR1 GAD1 GCLC GFRA2 GNAL GNPAT GPR85 GRIA1 GRIA3 GRIA4 GRID1 GRIK3 GRIN1 GRIN2D GRM3 GRM4 GRM5 GRM7 GULP1 HLA-DRB1 HOMER2 HSPA12A HTR1A HTR2A HTR6 HTR7 IFNG IMPA2 IPO5 JARID2 KCNH2 KCNN3 KREMEN1 LRRTM1 MAOB MAP4 MAP6 MCHR2 MCTP2 MEGF10 MLC1 MYL12B MYT1L NALCN ND2 NDE1 NDEL1 NDUFV2 NOS1 NPTN NRG1 NRG3 NRXN1 NTNG2 NUMBL PADI2 PCM1	

Table 3: Continued.

PCNT PDE4B PDE7B PGBD1 PICK1 PIK3C2G PIP4K2A PLA2G4C PLAA PLXNA2 PNPLA8 POM121L2 PPP1R1B PPP3CC PRKAG2 PRODH PRSS16 QK1 RAPGEF6 RELN RGS4 RPGRIP1L RSRC1 RTN4R SEMA3D SHANK3 SLC17A1 SLC17A6 SLC17A7 SLC1A2 SLC1A3 SLC1A6 SLC6A5 SLCO6A1 SMARCA2 SMARCC1 SNAP29 SPARCL1 SYN2 SYN3 SYNGR1 TAAR6 TCF4 TDO2 TRAF3IP1 TRMT2A TSNAX UFD1L USP46 VRK2 ZBED4 ZDHHC8 ZNF804A	GFAP MAP1B MAP2 MAP4 MYT1L NEFL TUBA1A TUBA1B
Oxidative stress	ATP5A1 ATP6V1A COX1 CRYM GCLC ND5 NDUFS3 NDUFV2 PRDX1 AKT1
AADAT ABCA7 ADAM22	ADAMTS4 ADIPOQ AGBL1 AKR1D1 AHI1 ALOX12 AP3D1 AP3M1 APOL2 APOL3 APOL4 APOL6 ARHGDIA ARID4B ASTN1 ATCAY ATP2B2 BAP1 BIVM BRD1 BTN3A1 CAD CAP1 CCDC60 CCDC141 CCKAR CDC42EP3 CEP63 CHL1 CHN2 CLU CNTNAP2 CPS1 CTNND2 DBP DDAH1 DZIP1 DNAJC6 DOCK9 DPYSL2 DRP2 EFNB2 EIF4A2 ENO2 ENTPD4 EPHA6 ERLIN1 ERMN FABP3 FARSA FBXL21 FIGN FNIP1 FOLH1 FOLH1B FOXP2 FSTL1 FTO FZD3 GAPDH GLRA2 GNPAT GMPS GPR18 GPR50 GPR125 HNRNPA2B1 HRH2 HS3ST2 HS6ST3 HSD11B1 HSPA8 HSPD1 ITIH4 KIAA0513 KREMEN1 LRRTM1 MMS22L MYL12B NCOA7 NLGN4X NOVA1 NR4A3 NRCAM NTNG2 NUBPL OLFM1 OPHN1 PADI2 PAK2 PAK3 PCDHA3 PDE7B PDE10A PGAM1 PGBD1 PGK1 PGP PNPLA8 PLXNA2 POMC POM121L2 PRKAG1 PRKAG2 PRKAG3 PYGB RAI1 RAPGEF6 RELN RIMS2 RIT2 RORB RSRC1 SEL1L3 SEMA3A SEMA3D SEPT4 GRIN2D SIM1 SLC32A1 SLC17A1 SLC17A7 SLC24A5 SLC25A14 SLITRK2 SMARCA2 SMARCC1

Table 3: Continued.

	SMARCE1 SPARCL1 SRD5A2 STRN TAAR6 TH1L TMTC4 TRIM3 UBAC2 UNC5C UGGT2 UQCRC1 USP46 UTRN YWHAZ ZBED4 ZBTB20 ZDHHC8 SLC39A12 KCNH7 ALDH1A3 MTNR1A BRPF1 EPB41L1 ZNF804A CYP26B1 NR4A2 HSD11B2 SLC6A9 AK1 HSPD1 OFCC1 ST6GAL2 MCHR2 MEGF10 ANKK1 PCDH11Y COX2 SEMA3B DGCR2 SLCO6A1 PICK1 ANK3 HSPA12A SLC25A14 TRMT2A ATP6V1B2 VRK2 PCDHA1 DRD1 ND2 ATP2A2 GSPT1 NALCN MCTP2 HTR2A CHRNA7 CSF2RA GRIA1 PLA2G4C RCAN1 SLC26A6 KCNE2 ACSL6 NOS1 BAI3 FAM8A1 ST7 DDO ASTN2 ERVWE1 GRM5 GNAL SEPT7 NBEAL2 GABRG1 GRIA2 KIF21A NCS1 ADSS JARID2 PSMD10 KCNH2 NUMBL RIC3 BRPF3 MBLN2 SPA17 KCNN3 SLC1A6 LSAMP RPGRIP1L SETD2 ABCA13 PIK3C2G GRM7 AP3B2 IPO5 JAG1 NRXN3 ATF7IP UFD1L MAGEL2 PCDH12 KIF13A NEFH DGKI CYFIP1 ALDH3B1 RLBP1 MCF2 SLC17A6 MAP6 NDUFS1 TCF4 SNX6 PPP3CC SGCE ME3 ORC3 C1QTNF3 TRAF3IP1 VIM BPRF3 ATP6V0D1 DCDC2 PPT1 KCNJ9 WDR1 HSPA8 CRYAB SLC1A2 APP TMEM200A CLINT1 HDAC9 PAICS MTIF3 NPTN PPP1R1B GPR85 NR3C1 QK1 PLAA PURA EIF3D SMG6 ASTN2 PRKAR2A MPDZ SC5DL
HERV-W no filter Number of SZ genes = 13 CACNG2 CYP1A2 DISC1 DTNBP1 HLA-DRB1 MAD1L1 MED12 MYO18B NOS1 NRG3 SHANK3 SP4 XRCC1	**Human gene products** Glutamate related GLUL Synaptic SPTNB5 GNB2 SHANK3 PDZRN4 DISC1 related DISC1 Neuregulin and growth FLT4 NEURL4 NLGN4X NRG3 Myelin related MYL6B Oxidative stress ATP11A COX11 Channels Calcium CATSPERG CACNG2 ITPR3 Potassium KCNN1 KCNJ16 Oxidative stress PYROXD2 Immune /cytokine CIITA DEFA7P TNFAIP3 CSF3R Structural COL6A3 DNM2 MYO18B MYBPC1 Signalling PDE4C PLA2R1 PLCB3 PLHDA2 PLA2G4A PRICKLE1(wnt) ABCA2 ABCA5 ABLIM3 ADAM29 ADAMYTSL2 AIM1L AKR1B15 ALG9 ANKRD11 ANXA1 ARID2 ARSE BET1L CCDC51 CENPE CEP152 CDH11 CHD23 CYFIP1 CYP1A2 DHTKD1 DPYSL5 DST EDC4

Table 3: Continued.

	ERV3 ERVWE2 EXOC5 FAM65A FBN1 FBN3 FEM1A GPSM1 HELB HERV-V1 HERV-V2 HIRIP3 HSD3B7 HSPD1 INTS2 IPO4 ITGB6 KIAA1731 KRTAP12-1 LAMB2 LOC100288413 LPHN2 LRP2 MAD1L1 MAU2 MBOAT1 MED12 MED12L MINPP1 MMD2 MUC12 NAP1L5 NEB NCAPD3 NDC80 NXPH1 OAS1 PCDHB5 PCDHB6 PCYT1B PDMD3 PHF3 PPYR1 PRDM10 PRMT2 PRSS22 PSMC4 PTPRU RABAC1 RGL1 RRM1 RG9MTD3 RIMBP3 RIMBP3B RNF213 RUNDC3B RXFP3 SARM1 SCAMP3 SHH SP4 SKIV2L2 SLC28A3 SLK SMC2 SPXW5 SRGAP1 STIM2 TCHH TERT TEX11 THEM5 TIMM44 TRIM39 TKTL1 TMEM11 TMF1 TP63 TRAK1 TRIM39R TRIM47 TSHR TTC18 USH2A USP31 VMAC VPD13D WDR20 WDR62 WNK2 XIRP1 XRCC1 ZBTB6 ZDHHC11 ZKSCAN2 ZNF34 ZNF99 ZNF355P ERVWE1 PSMC1 VPS13B SSX10 INTS8 OGN KLHDC8A HPS1 PAQR6 RUFY1 ASPM TTN GNA12 CPSF2 FBXW5 DTNBP1 DISC1 ARGLU1 FAM49B LSM14B CKAP5 UTRN ERVFRDE1 SH3TC1 HELT ANKFY1 SNAP47
Influenza: no filter Number of SZ genes = 24	**Dopamine related** DRD1 DRD2 D(1A) dopamine receptor DRD2 DRD4 DRD5 SLC5A3 **Serotonin** HTR1B HTR1D HTR5A SLC5A4 **Glutamate receptors and release** GLUR1 GRIA1 GRIK1 GRIN3B **Synaptic**

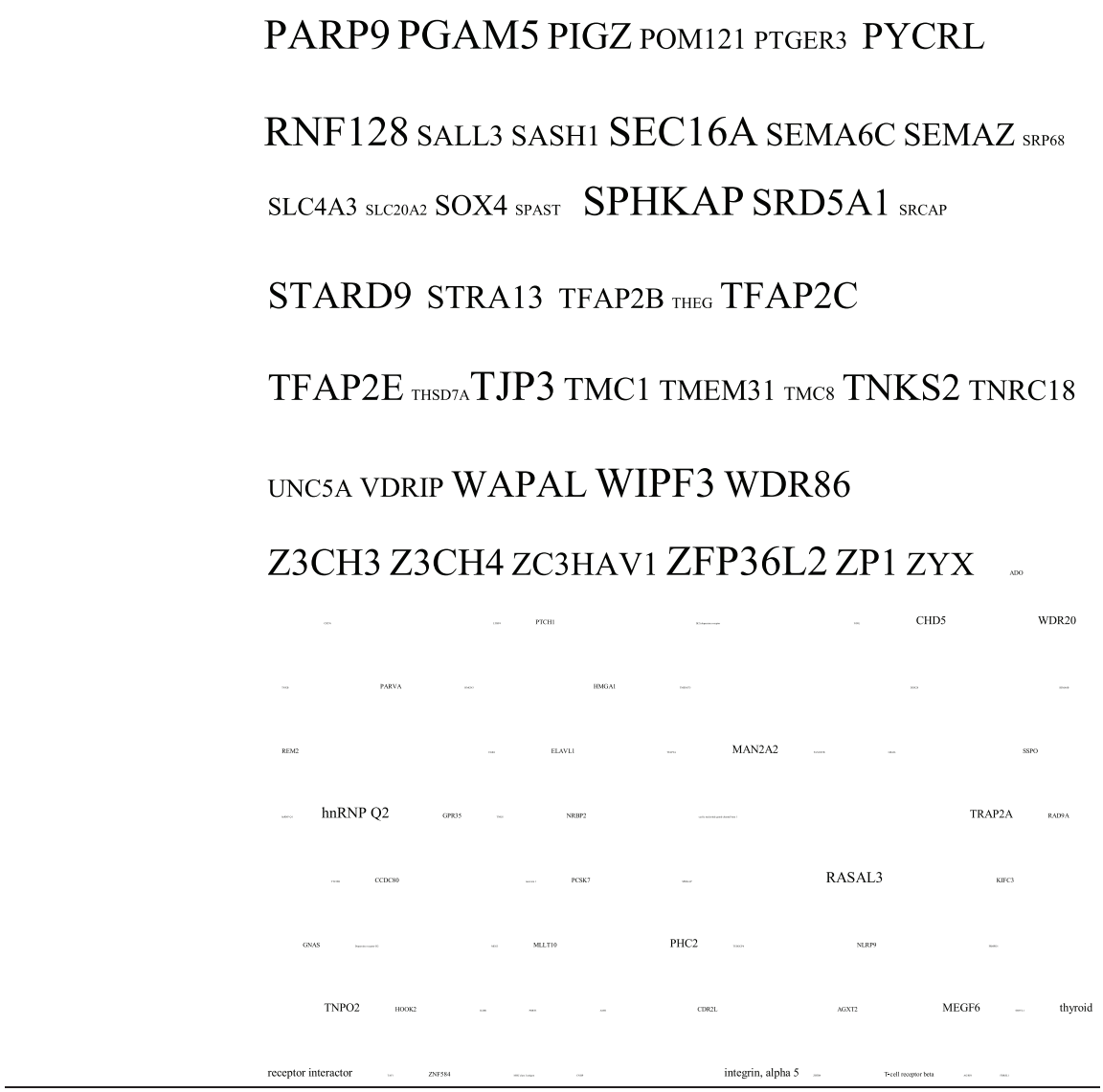
Table 3: Continued.

ACE CACNA1C DISC1 DRD2 DRD4 DRD5 ERBB3 GNAO1 GRIA1 HLA-DRB1 HTR1B HTR5A IL4 IPO5 KREMEN1 LRRTM1 ND2 NOS1 NRG1 NRG2 PCNT PNPLA8 PSEN2 SLC40A1	PDZRN3 syntaxin 16 Neuregulin and growth ERBB3 NRG1 NRG2 UTRN **DISC1 related** DISC1 PCNT Translation initiation EIF3A EIF3K EIF4G2 Oxidative stress ACOX2 cytochrome c oxidase subunit II NADH dehydrogenase subunit 1 NADH dehydrogenase subunit 2 Glycine receptors GLRA1 GLRA2 GLRA3 GLRA4 **Calcium** voltage-dependent L-type calcium channel subunit **Immune/cytokine** NFATC4 TNFRSF1B TLR4 TNFSF10 immunoglobulin heavy chain IFT122 Signalling NFKBIL2 PIK3CA SOS1 Structural ACTRT2 COL6A5 ABCB6ACE ACTRT1 ADNP AKAP6 ANXA1 ANXA4 APOBEC1 APIG2 AQP7 ARMC7 ASB1 BAT2L1CCDC135 CCS CCT6B CDC14A CDKL3 CENPA CEP192 CNGA4 CNOT1 CNTNAP5 CP CREG2 CRIM1CRIPAK CSE1L DCLRE1A DDX5 DENND3 DOCK1 EDNRA EFHC1ECHDC2 ESYT1 EXOC6 FAM123A FCHSD1 FUBP1GCNT6 GLT8D2 GLTSCR1 GNAO1 GPR153 GSDMD HTT IPO5 ISM2 KIFC2 KREMEN1 KRT76 LIPN LRRTM1 LRRC61 LRRC14BLRRIQ1 MAN1B1MAP7D1 MBOAT7 MRAP MTMR2 MGAT5B NOP58 NR2F6 NWD1 PLEC PHC3 PHLPP2 POM121L12 PPFIA4 PRL PRX RAB15 RBPJ RPM12B RSPH9 RHOBTB2 SCAPER SEC22A

Table 3: Continued.

	SENP7 SIPA1L2 SLC22A15 SLC26A9 SLC40A1 SMTLN1 SNAI1 SNTG1 STAC3 TABC1 TAS2R20 TCHH TMEM63A TMEM143 TMEM163 TMIGD2 TM4SF4 RSPH9 ANKLE2 TTN RAB8A TAS2R31 TRIM33 TROAP TYK2 SPC25 THADA UPF2 UBR3 UMODL1 LOXHD1 AP1G2 PNPLA8 XPO5 ZFP2 ZNF219 ZFPM1 ZNF391 LIPF COL6A6 NF1 PSEN2 PARN DLEC1 PIAS2 GTPBP1 calcium channel, voltage-dependent, L type, alpha 1C subunit PRKIP1 SNRK GAS6 IL4 TMTC4 GNA11 HOMER SPTY2D1 DNAH8 AIM1 PKD2L2 T calcium channel alpha 1G TTC25 TAS2R46 GRID2IP
Rubella: no filter Number of SZ genes = 21 DISC1 DRD2 DRD4 EGR4 ENAH ERBB2 FLNB GNAS GRIK2 GRIK3 GRIK4 GRIN2B GRIN2D HLA-A HLA-B HLA-DRB1 NOS1 NRG2 NRXN1 PRODH SHANK3	Cholinergic CHRNA3 ACHE Dopamine receptors dopamine receptor isoform short DRD4 Serotonin receptors HTR3C HTR3D Glutamate receptors GRM2 gluR7 GRIK2 GRIK3 GRIK4 GRIK5 NMDA receptor subunit epsilon 2 NMDA receptor subunit epsilon-3 NMDA receptor subunit epsilon-4 PRODH GLUR7 GABA GABA transporter 1 Synaptic GRASP HIPK4 SYNPO PDZD7 SHANK3 SYNCRIP DISC 1 related DISC1 Neuregulin and growth erbB-2 NRG2 GDF1 IGFBP3 Translation initiation EIF3A E2F1 Channels Calcium CACNAB1 CACNA1E Signalling GRB10 RASSF7 INPPL1 PTPRK PPP1R14C MAPK13 Immune cytokine HLA-A HLA-B MDR/TAP IL17D Structural ACTN4 COL1A1 COL7A1 MYH14 ABTB2 ADAMTSL5 ADRA1D AKAP5 AKNA AIPL1 ARHGAP30 BAALC BST1 CECR6 CHAC2 CKAP4 CTDP1 DCAF8L2 ENAH EPN3 FARS2 FLNB HCG4P6 HMGN1 INA IQSEC2 ITGA8 ITGB4 KLHL4 KLHDC4 LARP1 LEMD2 MED23 MFSD6 MON1B MRVIL MYO1B NCRNA00265 NSAP1 NTN1 NXF5 OPMCL OS9 OTOP1

Table 3: Continued.



therefore appear to be interdependent. The pathogens may promote disease if the human genes encode for homologous products, and the genes promote disease if the homologous pathogen is encountered. Such interdependence likely explains the heterogeneous data in both gene and risk factor association studies.

Other pathogens, including Borrelia Burgdorferri and T. Gondii have also been implicated in schizophrenia. These too express many homologous proteins to both viral and human proteomes. These parasites tend to be associated with schizophrenia in adulthood, while viral infections are predominantly prenatal risk factors. These may have primed the antibody network to respond to homologous antigens expressed by Borrelia or T. Gondii, suggesting that detection and elimination of these pathogens may be of therapeutic benefit in adult life.

Schizophrenia is a neurodevelopmental disorder [129, 130] and, as the risk-promoting effects of viruses are related to maternal infection, it is possible that knockdown or interference of foetal proteins by viral-induced antibodies targeting their human counterparts may contribute to the neurodevelopmental disturbances observed in schizophrenia. Indeed DISC1, neuregulin, ERBB4, FEZ1 or COMT knockout mice display many of the pathological and behavioural symptoms associated with schizophrenia [131–135]. Viral interference with these same proteins might be expected to promote the same effects, but on a massive scale, targeting many relevant proteins at once. It is also possible that such autoantibodies play a role in the comorbid conditions associated with schizophrenia, for example autoimmune disease such as Thyrotoxicosis, celiac disease, acquired haemolytic anaemia, interstitial cystitis, or Sjogren's syndrome [136].

Autoantibodies to several proteins have been reported in schizophrenia (muscarinic, nicotinic, dopaminergic and NMDA receptors, *inter alia*, (Table 2) and all are homologous

Table 4: Viruses reported to bind to DISC1 interactome partners.

DISC1 partner gene symbol	Protein name	Viral binder
ACTG1	Actin, cytoplasmic 2	HIV-1 [97] HSV1 [98]
ACTN2	Actinin, alpha 2	Hepatitis C [99]
AKAP9	A-kinase anchor protein 9	Epstein-Barr [97]
ATF4	Cyclic AMP-dependent transcription factor ATF-4	HSV1 [98]
ATF5	Cyclic AMP-dependent transcription factor ATF-5	HTLV1 [100]
BICD1	Protein bicaudal D homolog 1	Cytomegalovirus [101]
C14orf135	Uncharacterized protein C14orf135 precursor	Hepatitis C [102]
DCTN1	Dynactin-1	HSV1 [98]
DCTN2	Dynactin subunit 2	Dynactins are involved in the transport of the adenoviruses, HSV-1, the hantaan virus, HTLV-1 and the poliovirus [103–108]
DNAJC7	DnaJ homolog subfamily C member 7	Part of a complex forming the coxsackie virus receptor [109]
DYNC1H1	Dynein heavy chain, cytosolic	Adenovirus (in a complex with dynactin and NDEL1) [110]
EEF2	Elongation factor 2	Epstein Barr [111]
EIF3S3	Eukaryotic translation initiation factor 3 subunit 3	Hepatitis C [112]
FEZ1	Fasciculation and elongation protein zeta 1 (zygin I)	JC Polyomavirus [113]
HERC2	HECT domain and RCC1-like domain-containing protein 2	Papillomavirus 16 [114]
KIF3C	Kinesin-like protein KIF3C	HIV-1 [115]
MATR3	Matrin-3	HSV1 [98]
NDEL1	Nuclear distribution protein nudE-like 1	Part of a complex involved in Adenovirus transport (with dynactin and cytoplasmic dynein) [110]
PAFAH1B1	Platelet-activating factor acetylhydrolase IB subunit alpha	Binds to Poliovirus P3 protein and HIV-1 Tat [116, 117]
PCNT	Pericentrin	Involved in the microtubular transport of the adenovirus [118]
PGK1	Phosphoglycerate kinase 1	Epstein-Barr [119]
SMARCE1	SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily E member 1	HSV-1 [97]
STX18	Syntaxin-18	Papillomavirus [119]
TNKS	Tankyrase-1	Epstein-Barr [120]
TUBB	Tubulin beta chain	Epstein-Barr [119]
YWHAE	14-3-3 protein epsilon	Hepatitis C [97] : L : Epstein-Barr [119]
YWHAQ	14-3-3 protein theta	HIV [97] HSV1 [98]
YWHAZ	14-3-3 protein zeta/delta	HSV1 [98] : Epstein-Barr [119]

Table 5: The number of schizophrenia gene products in KEGG pathways related to immunity, and viral or pathogen life cycles.

Pathogen pathways		Viral pathways		Immune	
Toxoplasmosis	16	Focal adhesion	20	Cytokine-cytokine receptor interaction	26
Chagas disease	15	Cell adhesion molecules (CAMs)	19	Jak-STAT signaling pathway	16
Amoebiasis	13	Regulation of actin cytoskeleton	17	Systemic lupus erythematosus	13
Leishmaniasis	12	Protein processing in endoplasmic reticulum	13	T cell receptor signaling pathway	13
Viral myocarditis	8	Endocytosis	12	Phagosome	12
Staphylococcus aureus infection	7	Phagosome	12	Allograft rejection	11
Epithelial cell signaling in Helicobacter pylori infection	6	Gap junction	11	Hematopoietic cell lineage	11
Malaria	6	Tight junction	11	Antigen processing and presentation	10
Tryptophan metabolism	6	Adherens junction	6	Fc epsilon RI signaling pathway	10
NOD-like receptor signaling pathway	4	ECM-receptor interaction	6	Apoptosis	10
Vibrio cholerae infection	4	Oocyte meiosis	5	Graft-versus-host disease	9
Bacterial invasion of epithelial cells	3	SNARE interactions in vesicular transport	4	Autoimmune thyroid disease	8
E.coli infection	3			Chemokine signaling pathway	8
RIG-I-like receptor signaling pathway	3	Basal transcription factors	3	Leukocyte transendothelial migration	8
Cytosolic DNA-sensing pathway	2	Spliceosome	2	Natural killer cell mediated cytotoxicity	8
Shigellosis	2	Aminoacyl-tRNA biosynthesis	1	Adipocytokine signaling pathway	7
		Base excision repair	1	Asthma	7
		RNA degradation	1	Intestinal IgA production	5
				Toll-like receptor signaling pathway	5
				Complement and coagulation cascades	4
				B cell receptor signaling pathway	3
				TGF-beta signaling pathway	3
				Lysosome	2
				Regulation of autophagy	2
				Fc gamma R-mediated phagocytosis	1
				Primary immunodeficiency	1

to proteins expressed by the risk factors in schizophrenia. The effects of antibody knockdown have not been analysed for any schizophrenia related proteins, but have been reported for the microtubule-related protein *tau*, in relation to Alzheimer's disease. In mice, *tau* immunisation produces *tau* hyperphosphorylation, neurofibrillary tangles and axonal damage as seen in the human condition [137]. *Tau* (MAPT) is homologous to Herpes simplex (HSV-1) and a number of other pathogens. Such effects are relevant to the autoantigens observed in schizophrenia.

Schizophrenia is also a degenerative disease in adolescence or adulthood, characterised by oligodendrocyte cell loss, impaired synaptic connectivity and pyramidal cell dendrite shrinkage [41, 138–140], In the light of the above homologies it seems likely that such degenerative changes may relate to autoimmune-related attack of these diverse compartments. Indeed there is evidence for microglial activation in the schizophrenic brain [141] and several studies have reported changes in the cytokine profile in the brain, CSF or peripheral immune compartments [24, 142–146].

Table 6: Human homologues of Norwalk virus proteins.

Dopamine metabolisers	Amine transporters	Others
AOC2 amine oxidases		
AOC3""		
KDM1A amine oxidase demethylase		
KDM1B""		
MAOA monoamine oxidase	**SLC6A2** (**Noradrenaline**)	
MAOB""	**SLC6A3** (**Dopamine**)	**CADPS2 amine release activator**
RNLS renalase amine oxidase	**SLC18A1vesicular monoamine**	**CDCA7 cell division cycle associated 7**
SMOX spermine oxidase	**SLC18A2**""	**CDCA7L**
SPR sepiapterin reductase	**SLC22A2 organic cation**	**IL4I1 cytokine**
Monoamine synthesis cofactor	**SLC22A3 extraneuronal monoamine**	**PICK1** postsynaptic scaffold
SULT1A1 sulphotransferases	**SLC29A4** (Na^+/H^+)	
SULT1A3 monoamine metabolite sulphation		
SULT1A4		

3.8. Clinical Implications in Schizophrenia and Other Conditions. These data suggest that susceptibility gene products are the vehicles enabling the risk-promoting effects of pathogenic risk factors, via the interactions described above, and that the two are indispensable for the genesis of schizophrenia. Pathogen detection and elimination or vaccination, particularly prior to pregnancy might be expected to reduce the incidence of schizophrenia and also to be of clinical benefit in adulthood. Interestingly, vitamin D is able to stunt the growth of T. Gondii [147] and low levels of this vitamin, both prenatally and in adulthood, have been associated with schizophrenia risk, although abnormally high levels are also a risk factor [148]. Pharmaceutical effort in this direction may also vastly improve the armoury and safety of drugs against parasites such as T. Gondii and Borrelia.

Autoimmunity, involving several key schizophrenia-related proteins may well be a consequence of pathogen infection, and related to viral/human protein homology. Antigen and antibody removal by immunoadsorption techniques might therefore also be if clinical benefit.

This scenario suggests a novel and probably common class of "pathogenetic" autoimmune disease caused by pathogens but dependent on our genes. Indeed, the same phenomenon has been observed in Alzheimer's disease where the risk factor herpes simplex expresses proteins containing peptide matches to the products of multiple susceptibility genes [128]. Work from Kanduc's laboratory has also shown that 30 viral proteomes, including many nonretroviruses, contain multiple pentapeptide matches to many human proteins [149]. This is corroborated by data posted at http://www.polygenicpathways.co.uk/blasts.htm which shows, *inter alia*, that Bornavirus proteins, a virus implicated in Bipolar disorder [150], display this type of homology in relation to Bipolar disorder susceptibility gene products, that the coronavirus implicated in Parkinson's disease [151] expresses proteins homologous to the PARK7 gene product and to dopaminergic and oxidative stress-related proteins, and that multiple sclerosis autoantigens are homologous to the products of the Epstein-Barr virus which has been implicated in this disorder [152]. Our genomes and polymorphisms determine which vatches we possess, which pathogens match these sequences and which pathogen-related disorder we might develop. Environmental variables, and vaccination, determine which pathogens we encounter and our immune system (HLA-antigens and immune background determined soon after birth) may determine how we deal with these pathogens. With the power of current day bioinformatics, it should be possible to rapidly identify all vatches in the human proteome and to pair them with the various pathogenic species and human diseases. This would greatly aid our understanding of the implication of pathogens in disease and may lead to radically new therapies and prevention strategies in many disorders.

References

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