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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Abstract

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.
HERV-W 125 hits
Influenza 202 hits
Rubella 304 hits
Rhinovirus 284 hits
HSV-2 242 hits
Chromosome 10 versus viral prot 119857 hits

Figure 1: Continued.
Filter = schizophrenia

HERV-W 2533 hits

Rhinovirus 9452 hits

Varicella 12574 hits

HSV-2 14088 hits

Rubella 9452 hits

T. Gondii 11458 hits

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.

(a) Varicella virus vatches within DISC1

Figure 2: Continued.
Figure 2: Continued.
Multiple virus patches within DISC1

Figure 2: Continued.
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/keggsgenes.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

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

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

3.3. Viral Proteins Are Part of the DISC1 Interactome. DISC1 and many of its binding partners, or other members of
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 viruses 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].
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/kegggenes.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]:       | Mumps or cytomegalovirus infection (0–12 years old) [77] | HSV-1 seropositivity related to grey matter volume [78] |
| Influenza (first trimester) [13]:     |                         | HSV-1 (in Afro-Americans) or HHV-6 seropositivity: Inverse correlation with HSV-2 and cytomegalovirus [79] |
| Influenza or common cold with fever (second trimester) [16] |                         | |
| Poliovirus (second trimester) [17]:   | Coxsackie B5 infection perinatally [18] | Borna disease virus seropositivityvty [81] |
| Measles, Varicella zoster or polio (seropositivity at birth) [14] | Childhood meningitis (0–4 years old) [80] | |
| 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] | |

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] | Rhinovirus T. Gondii Varicella Rubella Herpesvirus 2 |
| CHRM1 Muscarinic cholinergic receptor [90] | Herpesvirus 2 Varicella Borrelia Influenza T. Gondii Rubella |
| DRD2 Dopamine receptor [82] | Varicella Herpesvirus 2 Varicella Rubella Rhinovirus T. Gondii |
| GRIN1 NMDA receptor subunit [91] | T. Gondii Herpesvirus 2 Influenza Varicella Borrelia Rubella Rhinovirus |
| ELANE Leukocyte elastase [92] | Varicella Rubella Borrelia Influenza T. Gondii Rhinovirus |
| OPRM1 Opioid receptor [93] | Rubella Borrelia Influenza Herpesvirus 2 Borrelia |
| NGF Nerve growth factor [92] | Influenza Herpesvirus 2 Borrelia |
| HTR1A Serotonin receptor [93] | Influenza Herpesvirus 2 T. Gondii Rubella Borrelia Varicella |
| HSP60 Heat shock protein 60 [94] | Rhinovirus Influenza Herpesvirus 2 Varicella T. Gondii |
| HSPA1A Heat shock protein 70 [95] | Rubella Influenza Herpesvirus 2 Varicella T. Gondii |
| HSP90 Heat shock protein 90 [95] | Herpesvirus 2 Rubella T. Gondii Influenza Rhinovirus |
| PAM/MYC [94] | Rhinovirus Varicella Herpesvirus 2 |
| S100B [96] | Rubella T. Gondii Borrelia Herpesvirus 2 |
| STRN Striatin [96] | |

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    | Dopamine related ALDH1A2, DDC, DRD2, DRD5 |
| Filter    | Serotonin related HTR1A, HTR2A, HTR3A, HTR3B |
| “schizophrenia” | Glutamate related DAO, GRIA2, GRIA3 |
| Number of SZ genes = 103 | GRIA4, GRID1, GRIN2A, GRIN2D, GRIN3A, GRIK3, GRIK5, GRM3, GRM7, Synaptic, CASB1, CPLX2, OTM8P1, DRP2, GRIP1 |
|           | RPIGRIP1L, HOMER1, HOMER2, HOMER3, HIPK3, SPTAN1 |
|           | SYN2, SYN3, RGS9, SNX6, GABA related, GABRB1, GABRG1 |
|           | GABBR1, Cholinergic, CHRFA1, DISC1 related, ATF7IP |
| DISC1 FEZ1 MLC1 PC1 PCNT | Myelin related, MBP, MOG |
|           | MPZL1, NOTCH4, Translation initiation, E1F3D, EIF4A2 |
|           | Neuregulin and growth, EGR4, GFRA1, CSF2RB, NFRA3, NRXN1 |
|           | NLGN4X, RET, UTRN, Oxidative stress, NXXV2, ATP2A2, CBR1 |
| NDUFS1 Channels Calcium, CACNA1B, CACNG2 | Sodium |
|           | NALCN, Potassium, KCNH2, KCNH7, KCNH8, KCNN2, Immune/cytokine, LIF |
| TPI1 Structural MAP1A, MAP1B, MYO1D, MAP1B, TBCB, TUB2A, Signalling |
|           | DKG1, GNB1, IMMT, PDE10A, PIK3C2G, P14KA, PAK3 |
|           | PPP3CC, GNA12, RAPGEF6, RASF7, STK24, DiGeorge, DGCR14 |
| ABCA7 ADAM28 AHI1 ANG2 ANK3 ANKHDF1 APOL4, APP |

ACSM1, ASH1, ALDH1A2, AK3, ARHGDAP18, ARHGEF10, ARCFP, ASTN1, BRD5, CACNG2, CHRFAA1, C11orf30, CLN14, CPLX2, CSF2RB, CSTN1, CTNNB1, DAO, DOK1, DISC1, DPP2, DPP4, DTPNP1, EGR4, FEZI, GABRB1, GFRA1, GFRA5, GNPAT, GPC1, GPR80, GRIA2, GRIA3, GRIK3, GRIN2A, GRIN2B, GRM3, GRM4, GRM7, HDAC4, HIPK3, HIST1H2A, HIST1H2AH, HLA-DQ8, HOMER1, HOMER2, HOMER3, HIPK3, HTRA5, HTRA7, IMP2, JARID2, KCNN8, LIF, MAPT, MCM16, MCTF12 MD505, MD510, MLC1, MOG, MPZL1, MUTED, NALCN, NDUFV1, NDUSD1, NOS1, NOTCH4, NRG1, NRG2, NRXN1, NTNG2, PCDH, PDGFR, PDLG, PIK3CG, PLXNA2, PPP3CC, PRS16, QKI, RAPGEF5, RELN, RAPGRAP1L, RDR1, SLC1A2, SRY, STIBSA1, STPL1AZ, SYN2, SYN3, TAARS, THYHA1, ZNF828A |
| 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 |
| MCHR1 MDGA1 MCTP2 MTIF3 MUTED NC5C NBEAL2 |
| PAFAH1B1 PAICS PCDHA1 PCDH11Y PLXNA2 PRNP PRSS16 |
| PTGFRN RAHI RSRC1 SEL1L3SEMA3A SIGMAR1 SIRPB1 |
| SLC25A3(NOx) SLC30A1(anion) SP4 STXBP1 STXGAL2 STRN SULT4A1 |
| TAAR6 TKT TMTC4 TPM1 UCHL1 UGTT2 WDR1 |
| SPRY4 SSTR2 YWHAH ZBT20 ZNF184 ZNF804A |
| HIST1H2AG TMEM200C VAX1VAX1 VCP VCPVCP |
| SIGMAR1 SIGMA1 SIGMAR |
| SLC1A5(GLUT) GRID1 GRID2 GRIN1A GRIN1B GRM10 GRM4 |
| SLC1A1 SLC1A7(P04/glu) SLC1A3(GLUT) kmo GABA |
| Dopamine related COMT DDC DRD1 DRD3 DRD4 DRD5 TH PEMT |
| Filter Serotonin related HTR6 HTR7 HTR5A Glutamate related DAO DDAH GRI1A |
| “schizophrenia” |
| Number of SZ genes = 166 |
| SLC17A1 SLC17A7(P04/glu) SLC1A3(GLUT) kmo GABA |
| related GABRA1 GABBR1 Synaptic DLG4 DTSNBP1 HOMER1 HOMER2 NOS1AP |
| SY1 SYNGAP1 SYT11 DISC1 related DISC1 CTT FEZ1 FZD3 |
| NDE1 NDE1 PDE4B TSNAX Neuregulin and growth ALK EGR2 |
| ABCA13 ACSL6 ADAM12 ADCP1 ADSS ALH1 |
| ALDH1A2 ALDHDB1 ALK ANK3 ARHGAP18 ARVCF |
| ASTN1 ASTN2 ATP6 BRD1 |
| Gene Symbols | Description                  |
|-------------|------------------------------|
| BTN3A1, CACNA1C, CCDC60 | GFRA1 NRG1 NRG3 NRXN1 NTF3 NPTN FGFR14, C522R, NTNG |
| CCKAR, CDKN2A, CHN2 | Myelin related MAG, MPZL, NOTCH4, RTN4R Oxidative stress GCLM, ATP6 |
| CHRM5, CHRNA7, CIT, COMT, CSF2RA, CSF2RB, CSPG5 | ND2 Channels Calcium CACNA1C, Potassium KCN3, KCNH2 |
| CYTB, DAO, DA0A, DBH, DGCR2, DGCR6, DISC1, DKK4, DLG4, DLX1, DRD2, DRD3 | Immune/cytokine IL1A, MICB, TRAF3IP1, Structural MAP4, MAP6, MYH9 |
| DRR4, DRR5, DTNBP1, EOR2, ENO2, FBX1, FEZ1, FGFR4 | MYT1L Signalling ARHGAP18, ARHGEF10, GNAL |
| FXR1, FZD3, GABBR1, GABRA1, GABBRP, GCM, GFRA1, GNAL, GNB1L, GNL3, GRIA3, GRIA4, GRID1, GRID2, GRIN2D, GRM3, GRM4, GRM5, GRM7, HISTH1DAG, HISTH1IAH, HOMER1, HOMER2, ILSA12A, HTTR2, HTTR2C, HTTR3A, HTTR6, HTTR7, IL1A, IMPA2, JARID2, KCNQ1, KCNQ3, KMO, MAG, MAP4, MAP8, MAPK14, MCM5, MCTP2, MDA5, MEGF10, MCB, MLC1, MPZL1, MUTED, MYH9, MYT1L, ND2, NDE1, NDE1L1, NFU1, NEUROG1, NOS1AP, NOTCH14, NPAS3, NPTN, NRG1, NRG3, NNXN1, NTF3, NUMBL, OPRM1, PADD2, PCDH8, PDE4B, PDE4D, PDLDM3, PMP12, PLAG2, PMA, PLOXNA2, PNO, PMI2L2, PPIK1B, PPIKCC, PRODH, PSS1, PTBP2, RAGA, RELN, RGS4, RPGRIPL1, RTN4R, SHL9A5, SIRT5 | UHMK1, DiGeorge, DGCR2, DGCR6 |
| ABCA13, ADAM12, ADSS, AHI1, ARVCF, BRD1, BT2NA2, CHN2 | CSPG5, DLX1, ENO2, FBCL21, FCYD6, GRP78, JARID2 |
| KPNA3, NPAS3, NUMBL, OPRM1, PCDH8, PLXNA2, PNPO, POM121L2 | PRSS16 |
| KPC1, LRR1, MBD4, MAP2K1, ML1, MLC1, NRCAM, NUDT14, PAX6, PRSS16, PTBP2, PTP1B, RAGA, RELN, RGS4, RPGRIPL1, RTN4R, SHL9A5, SIRT5 | YWHAZ, MUTED, SIRT5, HBB2, MAP2K1, MAP4, HIST1H2DJ |

**Influenza**

*Filter “schizophrenia”*

**Number of SZ genes = 167**

**Dopamine related**

**Serotonin related**

**GABA-related**

**Sympathetic**
| Table 3: Continued. |
|--------------------|

ACSL6 ADAM12 ADCYAP1  
ADSS AH1 ALDH1A2  
ALDH8B1 ALK ANK1  
ARHGAP18 ARVCF ASTN1  
ASTN2 ATP6 BRD1 BTN3A1  
CCDC6 CCKAR CDKN2A  
CHN2 CHRM5 CIRNA7 CIT  
COMT CSF2RA CSF2RB  
CSF5G CYTB DAO DAOA  
DBH DGRG2 DGRF6 DISC1  
DKK4 DLG4 DLX1 DRD2  
DRD3 DRD4 DRD5 DYNBP1  
EG2 E203 E2AP FEZ1  
FGF14 FXR1 JDD3 GABBR1  
GRABRA1 GABRB3 GCLM  
GFRP1 GNAL GNHL GN1L3  
GRIA3 GRIA4 GRDIV GRIN2A  
GRIN2D GRM3 GRM4 GRM5  
GRM7 HIST1H2AG  
HIST1H2AH HIST1H2AI  
HOMER1 HOMER2 HSPA1A2  
HTR1A HTR6A1 HTR2C HTR5A  
HTR6 HTR7 IL1A IMPA2  
JARID2 KCNN3 KCNMA1  
KCNQ1 MAP2 MAP3 MAP4  
MAPK6 MAPK14  
MCP1 MCTP2 MOGAA1  
MEGFI8 MCM11 MLCl MPZL1  
MUTED MYH9 MYT1L ND2  
NDE1 NDEF1 NDUFB2  
NEUROG1 NOS1AP NOTCH4  
NPSIA NPTN NRG1 NRG3  
NXXN1 NTG1 NTG2 NUMBL  
OPRM1 PAD2 PC1 PC4  
PDGFR PDGFRB P3M7  
PLA2G4C PLA2L PLXNA2  
PNNP POM12L2 PPP3R1B  
PPP3CC PRODH PRSS16  
PTBP2 RAPGEF5 RELN RGS4  
RPGRP1L RTN4R SIHAS5  
SIRT5 SLC17A1 SLC17A3  
SLC17A7 SLC18A3 SLC1A4  
SLC5A5 SMARCC1 SNAP29  
SN4 SPARCL1 SRR SYN2  
SYN3 SYNGR1 SYT1 TH  
TPH1 TRAF3P1 TSNAX  
TSPAN8 TUBA8 TXNDC5  
UPT1 UIMK1 VRK2  
YWHAE ZDHHC8 ZNF74  

SYNGAP1 SYNGR1 SYT11 DISC1 related CITNDE1PCM1PDH4B  
MLC1 TSNAX Neuregulin and growth ALK NRG1 CSF2RB GFRA1  
NEUROG1 CSF2RA EGR2 NTG1 NTF3 Myelin related MAG  
NOTCH4 MPZL1 RTN4R Cholinergic CHRM5 CIRNA7 Oxidative stress  
CYTB GCLM Channels Calcium CACNA1C Potassium KCNN3 KCNH2  
Immune/Cytokine IL1A TRAF3IP1 Structural MAP6 MYT1 Signalling  
ARHGEF10 GNL3 MAPK14PLA2G4C PPP3CC UHMK1 DiGeorge  
DGCR2 DKK4 YWHAE ZDHHC8 SPARCL1 MC5R ASNR1 CARN1 ASTN1  
ALDH3B1 ARVCF UFD1L PAPP3 SPINT5 SLC06A1ANION MCTP2  
FBCL21 JAK2 PCDH8 NRG1 NDE1 PLXNA2 CSPG5 TXNDC5  
CHN2 NPAS3 DLX1 FXR1 SP4 GRM1 ENO2 TSPAN8  
NUMBL SMARCC1 ZNF74 BDNF KPNA3 BTN3A1  
HIST1H2AG HIST1H2AH FABP7 HHR2 ACSL6 ADAM12 HIST1H2BI MDCB  
ADSS ARHGAP18 ABCA13 YWHAZ TAAR6 ADCYAP1 GRP38 PDK2  
ZNF804A
| Rhinovirus | Dopamine related DBH COMT DRD1 DRD2 DRD3 SLC18A2 |
|------------|---------------------------------------------------|
| Filter     | Serotonin related HTR1A HTR2C HTR6 HTR7 TDO2 Glutamate related DAO DAOA GRIN1 GRIN2A GRIK3 GRM4 GRM5 GRM7 SLC1A3(GLUT) SLC1A4(GLUT) SLC17A3 SLC17A7(P04/glut) GABA related GABRA1 GABRB2 GABBR1 Synaptic HOMER1 HOMER2 Rpgrip1L NOS1 NOS1AP SYNGR1 SYT11B54 DISC1 related DISC2 CIT |
| “schizophrenia” | |
| Number of genes = 176 | |
| ABCA13 ACSL6 ADAM12 ADCY10 ADSS AHI1 ALDH3B1 ANK3 ANKK1 APOL2 ARHGAP18 ARHGEF18 ARVCF ASTN1 ASTN2 BRD1 BTN3A1 C10orf129 CACNA1C CCKAR CHID1 CHL1 CHRFAM7A CHRM5 CHRNA7 CIT CLDN5 CLNT1 CLOCK CNP COMT CSF2RA CSF2RB CTSLA4 CTNNB1 DAO DAOA DBH DGCR2 DGCR5 DGCR6 DGK1 DISC1 DKK4 DLX1 DPYSL2 DRD2 DRD3 DRD4 DRD5 EGR4 ENO2 ESR1 FABP7 FEZI FGF14 FXR1 FXR3 GABBR1 GABRA1 GABBD2 GABRP GFRAS GNBI1 GNLI3 GNPAT GRIA1 GRIA3 GRIA4 GRIK3 GRIN1 GRIN2A GRIN2D GRM3 GRM4 GRM5 GRM7 HIST1H2B1 HILA-DRB1 HOMER1 HOMER2 ISPA12A HTR1A HTR2A HTR2C HTR6 HTR7 IL1A IMAP2 INTS6 ITIH3 JARID2 KCNH2 KPN1A3 LIF MAG MAP2 MAP6 MAPK14 MCSR MCHR1 MCHR2 MCT2 MDA1 MICB MLC1 MUTED MYB9 MYT1L ND2 NDL1 NDUFB2 NOS1 NOS1P1 NOS1P2 NOS1P3 NT5D1 NPY NOS2 NOS3 NOS3P1 NPAS3 NPTN NR1G1 NR2G3 NRXN3 NT5F3 NQSL OPML OPCML OPMM1 PAD12 PC1 PC2 PC4 PC5 PC8 PC9 PDE4B PDE7B PDLIM5 PN4 PLAA PLAC8 PNA08 PLACA2G4C |
| NTF3 | Myelin related MAG NOTCH4 Cholinergic CHRNA7 CHRFAM7A Oxidative stress ALDH3B1 ND2 ND4 NDUFV2 Channels Calcium CACNA1B |
| NRG1 NRG3 NTN1 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 PLACA2G4C |
| VRK2 DiGeorge DGCR2 DGCR5 DGCR6 __ __ ABCC1 ITIH3 JARID2 |
| FXR1 __ PADI2 GNBI1 ORC3L SIL1 __ ZNF69A RELN __ DKK4 ADGAP1 POM121L2 |
| ADSS __ ISPA12A __ PFFCC __ MYIN INTS6 __ ESR1 PB1 TMEM108 __ PFN4 |
| CHL1 AK1 __ __ CLOCK PNPO SPARCL1 __ OPCML ZDHHC8 __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __.__ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ __ ___
Table 3: Continued.

| Gene Symbol | Description |
|-------------|-------------|
| PNPO | Dopamine related |
| POM121L2 | COMT |
| PPP1R3B | DBH |
| PPP3CC | DRD3 |
| PRKCSH | DRR |
| PTBP2 | DRD5 |
| RAEGF5 | PEMT |
| RPTPL | ANKK1 |
| SHISA5 | MACF1 |
| MDGA1 | SIRT5 |
| PROC | ZBED4 |
| CTLA4 | ZNF71 |
| ZNF184 |  |

Rubella

Filter

“schizophrenia”

Number of genes = 179

Dopamine related genes: COMT, DBH, DRD3, DRD5, PEMT

Serotonin related genes: HTR1A, HTR2A, HTR2C, HTR5A, HTR7, HTR11

Glutamate related genes: DAO, DAOA, GRIA3, GRIA4, GRID1, GRIN1, GRIN2A

GRM3, GRM4, GRM5, GRM7, KMO, SLC14A1(GLUT), SLC17A3, GABA

Cholinergic related genes: GABRA1, GABBR1, GABRB2, GABRP

Chromatin related genes: CAV1, DTMN1, DPN1, LAMP1, SNAP29, SYN2, SYN3, RGS4

SYNGAP1, SYNGR1, SYT11, DISC1, PC1, PDE4B, NDEL1

FEZ1, FZD3, Neuregulin and growth genes: NRG1, ERBB1, ERBB3

ERBB4, GFRAL, NT3, NTNG1, FGF14, Myelin related genes: NOTCH4, RTN4R

QK1, Oxidative stress genes: CYTB, GCLM, ND2, NDUFV2, Channels, Calcium

Potassium related genes: KCNJ3, KPNAA3

Immune/cytokine related genes: TRAF3IP1, Structural

MAP6, MYT1L, Signalling related genes: ADCYAP1AK1, ARHGEF10, CDKN2A, GNAL

GNB1L, GNL3, MAPK14, IMPA2, PLAA, PLASG4C, RAPGIF3, PDE4D, PPP1R1B

DiGeorge related genes: DGCRI, DGCRI6

HIST1H2A, HIST1H2B, HLA-DRB1, HOMER1, HOMER2, HTR1A, HTR2A, HTR2C, HTR5A

JARID2, FXYD6, BTN2A2, NUMBL, ARVC, H4, ALDH1A2, ZNF804A
| Table 3: Continued. |
|---------------------|
| HTR6 HTR7 IL1A IMPA2 |
| JARID2 KCNN2 KCNQ3 KMO |
| KPNA3 KREMEN1 MAG |
| MAP4 MAP6 MAPK14 MC5R |
| CCKAR ASTN2 ASB5 AUTS2 FXR1 ASTN1 |
| TH HRH2 ADAM12 PCB2 ZNF74 YWHAZ |
| PER1 TUBA8 ARHGAP18 ENO2 SIN3 BRD1 ISMD2 GRP78 |
| TAAR6 HIST1H2B KREME1 SLC6A1 HIST1H2AH |
| PDLIM5 MDGA1 ADSS ZDHHC3 AHI1 OPRM1 DPP10 |
| MC5R DKK4 |

| Varicella |
|-----------|
| Dopamine related COMT DDC DRD2 DRD5 Serotonin related HTR2C HTR7 HTR3A HTR3D TPH2 TPH1 Glutamate related GRIN1 |
| GRIA2 GRIN2A GRIK1 GRIK5 GRM2 GRM7 SLC6A5(Gly) SLC17A6 |
| GABA –related GABRA5 GABBR1 Synaptic DLGAP2 |
| related DISC1 CIT FEZ1 PCNT POC1 PDE4B Neuregulin and growth NRG1 NRG3 |
| NT53 NTNG2 CSF2RA NRXN1 EGR2 NRXN3 NLGN4X |
| UTRN VGF Myelin related NOTCH1 OMG Cholinergic CHRM5 |
| CHRFAM7A Oxidative stress COX2 ND1 ND5 NDUFS1 QDPR Channels |
| Gene 1 | Gene 2 | Gene 3 | Gene 4 | Gene 5 | Gene 6 |
|-------|-------|-------|-------|-------|-------|
| GNPAT | GRIK3 | GRIN1 |       |       |       |
| GRIN2A | GRIN2D | GRM5 |       |       |       |
| GRM7 | HDAC3 | HDAC4 | HIKP3 |       |       |
| HLA-DRB1 | HTR2C | HTR7 |       |       |       |
| KCNHL | KREME1 | MAP6 |       |       |       |
| MAPK14 | MCHR1 | MCTP2 |       |       |       |
| MGB | MYT1L | NALCN |       |       |       |
| NEUROG1 | NOS1 | NOS1AP |       |       |       |
| NPS3 | PDE4B | P4KA | PLAA |       |       |
| PLENX2 | PLTP2 | RAPGEP6 |       |       |       |
| RPS6K1 | SEMA3D | SLC17A6 |       |       |       |
| SLC6A5 | SLC6A1 | ST4A |       |       |       |
| SPARCL1 | SULT4A1 | TAAR6 |       |       |       |
| TPH1 | TRMT2A | UHMKI | VRK1 | VRK2 | ZNF804A |
| Calcium | CACNA1C | Potassium | KCNH7 | KCNQ5 | KCNH2 |
| Immune/cytokine | IL1RAPL1 | IFR | Structural | NEFM | MAP1A | MAP1B | MAP6 |
| MYH | MYT1L | Signalling | CDC42 | GNB1 | DAG1 | DGKI | UHMKI | GUCY1A | PI4KA |
| PLAA | PKCG | PDE10A | RAPGEF6 | GSK3A | RASSF7 | VRK2 | DiGeorge |
| STAB1 | FUB1 | CPNE2 | AP3B2 | SULT4A1 | CELF4 | MICB |       | MGB1 |
| CNTNAP2 | AP3D1 | MCF2 | YWAH | ANKHD1 | PCDH11Y | PSMD19 | CASRD |       |
| SLC6A2(Ne) | ORC3L | PTBP2 | ZNF804A | CSPG5 | NCOA1 | NCOA7 | GDNF | PERSEPH |
| TRMT2A | TRIM3 | ZBER4 | RNH1 | ANKK1 | MBLN2 | SEMA3B | SLC26A5 |       |
| PLXNA2 |       | LAMB2 | HP1BP3 | TPM3 | ADAMTS4 | DPIYS2 | GUR1 |       |
| CLDN10 | NPAS1 | BRD1 | CTNS | HRH2 | BACE1 | ASI1 | ASGAP4 | GLY |
| DNAJC6 | AADAT | ALDH1A2 | retinoic | ITIH4 |       | DBP |       |       |
| DOCK9 | APOL3 | SPARCL1 | KIF13A | MECP2 | SIRPB1 | magel2 | TAAR6 | EPHA6 |
| ATP6V1A | NRCAM |       | LAMB2 | CAMKV | MCTP2 | PCDHA1 | UGTT2 | PADI2 |
| FN1P1 | KIF21A |       |       |       |       | ACOY |       |       |
| ABCA13 | SORBS1 |       | PTGRN | SEMA3D | PET |       | SLCO6A1 |       |
| SLC25A3 | SP4 | LANCL2 |       |       |       |       |       |       |

| T. Gondii | Dopamine related | COMT | DBH | DRD3 | DRD4 | PEMT | SLC18A2 | TH |
| Filter | Serotonin related | HTR1A | HTR2A | HTR2C | HTR5A | TPH1 | Glutamate |       |
| "schizophrenia" related | DAOA | GRIA4 | GRIN1 | GRIN2A | GRIN2C | GRIN2D | GRIK3 |       |
Table 3: Continued.

| Genes          | Description                      |
|----------------|----------------------------------|
| GRM3, GRM4, PROD1, KMO, SLC6A5(GLY) | GABA–related                |
| GABRP          | Synaptic                        |
| SYNGAP1, SYN2, SYN3, SNAP29, SYNGR1 | SYT11, RGS4, DISC1-related    |
| DISC1, FEZ1, FZD3, NDE1, PDE4B, GABRP | Neuregulin and growth         |
| ERBB2, ERBB3, EGR2, FGF14, NEUROG1, NTF3, NRXN1 | NTNG2, Myelin related |
| NTNG2          | MAG, MPZL1, QK1, Cholinergic, ChRNA7, Oxidative stress, ATP6, GCLM, ND2, NDUFB2, Immune/cytokine, IL1A, MICB, TRAF3, IPI, Signalling, ADCC, ARHGEF10, CDKN2A, GNA11, GNHL, ARHGAP18, MAPK14, GNB1L, PLA2G4C, PLA2G4C, PPP3CC | |
| PPP1R1B, RAPGAP6, UHMK1, VRK2 | Structural MAP4               |
| MYT1L, MYH9, TUBA8, DiGeorge, DGCR2, DGCR6 | Circadian, CLOCK, PER1       |
| AHI1, AK1, ALDH3B1, ANK1, ARVC, ASTN2, BRD1, BTN2A2 |                       |
| BTN3A1, CCDC60, CCKAR, CHN2, CSPG5 | DKK4, ENO2                 |
| FABP7, FYX6, GRP78, HIST1H2AH, HIST1H2AG, HIST1H2A, PHKPA3 |                       |
| KREME1, SMCC, MDGA1, MC5R, MCTP2, D2, CHRM1, NPAS3, PNP |                       |
| PTBP2, RELN, SHISA5, SIRT5, TAAR6, TSPAN8, TXNDC5 | YWHAZ, ZDHHC9, ZNF74        |

**Note:** Table contains a list of genes and their associated descriptions. The table is continued from a previous page.
| Borrelia | **Dopamine** ALDH1A2 DRD2 DRD3 DRD4 DRD5 MAOB |
|----------|-----------------------------------------------|
|          | **Serotonin** HTR1A HTR3C HTR6 HTR3D HTR3E SLC6A5 TDO2 |
|          | **Glutamate** DAOA GUL GRIA3 GRI4 GRIN1 GRIK1 GRIK3 GRIK5 |
|          | **GRIN2A GRM2 GRM3 GRM4 PRODH SLC1A3 SLC1A5 SLC1A4** |
|          | **GABA** GABBR1 GABBR2 GAD1 GAD2 **Cholinergic** |
|          | **CHRMP5 synaptic** BLOC1S1 CABIN1 CNTN4 CPLX2 |
|          | **DLG1 GPRASP2 GRIP1 HOMER2 HOMER3 RGS4 RGS9** |
|          | **SHANK3 SNAP29 SPTAN1 SYNGAP1 STXB1 SYNR1 SYN2** |
|          | **SYN3 SYT5 DISC1 related** DISC1 FEZ1 IMM |
|          | **MLC1 NDE1 NDEL1 PCM1 PCNT PDE4B TSNA** |
|          | **Neuregulin/ growth** EGR4 EGR2 ERBB4 FGF14 NRG1 NRG3 |
|          | **Immune** IL1R1L1 LIFR TPI1 Signalling CSNK1D GSK3A |
|          | **IMPA2 PIPK2A PLA2G4C PLA2G4D SH3GL2 STK24** |
|          | **Channels** CACNA1B CACNG2 KCNH5 KCNH6 KCNN2 |
|          | **Myelin** CNP MOBP OMG RTN4R **Structural** ACTB ACTG1 |

**Table 3:** Continued.
| Table 3: Continued. |
|---------------------|

| GFAP | MAP1B | MAP2 | MAP4 | MYT1L | NEFL | TUBA1A | TUBA1B |
|------|-------|------|------|-------|------|--------|--------|

**Oxidative stress**

| ATP5A1 | ATP6V1A | COX1 | CRYM |
|--------|---------|------|------|

| GCLC | NDS | NDUFS3 | NOVA1 | PRDX1 | ACT1 |
|------|-----|--------|-------|-------|------|

| 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 | CCO68 | CDDC1 | CCKAR | CDC42EP3 | CEP63 |
|------|--------|-----|------|-------|-------|-------|---------|-------|

| CHL1 | CHN2 | CLU | CNTNAP2 | CPS1 | CTNND2 | DBP | DDAH1 | DZIP1 |
|------|------|----|---------|------|-------|-----|-------|------|

| DNAJC6 | DOCK9 | DPYSL2 | DRP2 | EFNB2 | EIF4A2 | ENO2 | ENTPD4 |
|--------|-------|--------|------|-------|--------|------|--------|

| EPHA6 | ERLIN1 | ERMN | FABP3 | FASLA | FBXL21 | FIGN | FNIP1 | FOLH1 |
|-------|--------|------|-------|-------|--------|------|-------|-------|

| FOLH1B | FOXP2 | FSTL1 | FTOFZD3 | GAPDH | GLRA2 | GNPAT |
|--------|--------|-------|---------|-------|-------|-------|

| GMPS | GPR18 | GPR50 | GPR125 | HNRRPA2B1 | HRH2 | HS3ST2 |
|------|-------|-------|--------|------------|------|--------|

| HS6ST3 | HSD11B1 | HSPA8 | HSPD1 | ITIH4 | KIAA0513 |
|--------|--------|-------|-------|------|----------|

| KREMEN1 | LRRM1 | MMS22L | MYL12B | NCOA7 | NLGN4X | NOVA1 |
|---------|-------|--------|--------|-------|-------|-------|

| NR4A3 | NRCAM | NTNG2 | NUBPL | OLFM1 | OPN1 | PADI2 | PAK2 | PAK3 |
|-------|-------|-------|-------|-------|------|-------|------|------|

| PCDHA3 | PDE7B | PDE10A | PGAM1 | PGBD1 | PGK1 | PGPPNPLA8 |
|--------|-------|--------|-------|-------|------|------------|

| PLXNA2 | POMC | POM121L2 | PRKAG1 | PRKAG2 | PRKAG3 |
|--------|------|----------|--------|--------|-------|

| PYGB | RAI1 | RAPGEP6 | RELN | RIMS2 | RIT2 | ROB | RSRC1 | SEL1L3 |
|------|------|---------|------|-------|------|-----|-------|--------|

| SEMA3A | SEMA3D | SEPT4 | SIM1 | SLC32A1 | SLC17A1 | SLC17A7 |
|--------|--------|-------|------|---------|---------|---------|

| SLC24A5 | SLC25A14 | SLITRK2 | SMARCA2 | SMARCC1 |
### Table 3: Continued.

| Gene Symbols | Description |
|--------------|-------------|
| SMARCE1, SPARCL1, SRD5A2, STRN, TAAR6, TH1L |  |
| TMTC4, TRIM3, UBAC2, UNC5C, UGGT2 |  |
| UQCRCL1, USP46, UTRN, YWHAZ, ZBED4, ZBTB20, ZDHHC8 |  |

#### 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

- **CAONG2 ITPR3**
  - Potassium
  - KCNN1 KCNJ16 Oxidative stress

- **PYROXD2**
  - Immune /cytokine
  - CITA DEFA7P

- **TNFAIP3 CSF3R**
  - Structural
  - COL6A3 DNM2 MYO1B

- **MYBPC1**
  - Signalling
  - PDE4C PLA2R1 PLCB3 PLHDA2

- **PLA2G4A PRICKLE1 (wnt)**
  - ABA2 ABA5 ABLIM3

- **ADAM29**
  - ADAMTSL2 ARM1L AKR1B15 ALG9 ANKRD11 ANXA1

- **ARID2 ARSE BET1L CCDC51 CENPE CEP152**

- **CDH11 CHD23 CYR61 CYP1A2 DHTKD1 DPYSL5 DST EDC4**

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**HERV-W no filter**

- Number of SZ genes = 13

**CACNG2 CYP1A2 DISC1 DTNBP1 HLA-DRB1 MAD1L1 MED12 MYO1B NOS1 NRG3 SHANK3 SFP XRC1**
| Table 3: Continued. |
|---------------------|
| **ERV3**<sub>ERVW2E</sub> **EXOC5**<sub>FAM65A</sub> **FBN1**<sub>FBN3</sub> **FEM1A**<sub>GPSM1</sub> **HEL8**       |
| **HERV-V1****HERV-V2** **HIRIP3** **HSD3B7** **HSPD1** **INTS2** **IPO4** **ITGB6**          |
| **KIAA1731** **KRTAP12-1** **LAMB2** **LOC100288413** **LPHN2**                        |
| **LRP2**<sub>MAD1L1</sub> **MAU2** **MBOAT1**<sub>MED12</sub> **MED12L** **MINPP1**      |
| **MMD2**<sub>MUC12</sub> **NAP1L5**<sub>NEB</sub> **NCAPD3**<sub>NDC80</sub> **NXPH1**<sub>OAS1</sub> |
| **PCDHB5** **PCDHB6** **PCYT1B** **PDMD3**<sub>PHF3</sub> **PPYR1**                     |
| **PRDM10**<sub>PRMT2</sub> **PRSS22**<sub>PSMC4</sub> **PTPRU** **RABAC1**<sub>RGL1</sub> |
| **RRM1** **RG9MTD3** **RIMBP3**<sub>RIMBP3B</sub> **RNF213** **RUNDC3B**                |
| **RXFP3**<sub>SARM1</sub> **SCAMP3** **SHH** **SP4** **SKIV2L2** **SLC28A3** **SLK**        |
| **SMC2** **SPXW5** **SRGAP1** **STIM2** **TCHH**<sub>TERT</sub> **TEX11** **THEM5**        |
| **TIMM44**<sub>TRIM39</sub> **TKTL1** **TMEM11** **TMF1**<sub>TP53</sub> **TRAK1** **TRIM39R** |
| **TRIM47** **TSHR** **TTC18** **USH2A**<sub>USP31</sub> **VMAC**<sub>VPD13D</sub>         |
| **WDR20** **WDR62** **WNK2** **XIPR1** **XRCC1** **ZBTB6**<sub>ZDHHC11</sub> **ZKSCAN2** |
| **ZNF34** **ZNF99** **ZNF355P**                                                       |

| Influenza: no filter | Dopamine related | DRD1 | DRD2 | D(1A) dopamine receptor |
|----------------------|-----------------|------|------|-------------------------|
|                      | DRD2 | DRD4 | DRD5 | SLC5A3 | Serotonin | HTR1B | HTR1D |
|                      | HTR5A | SLC5A4 | Glutamate receptors and |
| Number of SZ genes = 24 | release | GLUR1 | GRIA1 | GRIK1 | GRIN3B | Synaptic |
| Gene                  | Description                                      |
|----------------------|--------------------------------------------------|
| 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 NFKB1L2 PIK3CA |
| SOS1 Structural     | ACTRT2 COL6A5                                   |
| ADNP AKAP6 ANXA1 ANXA4 APOBEC1 APIG2 AQP7 ARMC7 |
| ASB1 BAT2L1CCDC155  | CCS CCT6B CDC14A CDKL3 CENPA                    |
| CEP192 CNGA4 CNOT1  | CNTNAP5 CP CREG2                                |
| CRIM1 CRIPAK CSE1L  | DCLRE1A DDX5 DENDND3 DOCK1                     |
| EDNRA EFHC1 ECHDC2  | ESYT1 EX05 FAMILY FCISD1 FUBP1 GCNT6            |
| GLT8D2 GLTSCR1 GNAO1 | GPR153 GSDMD HTT IPO5 ISM2                      |
| KIFC2 KREMEN1 KRT76  | LIPN LRRTM1 LRRC61                              |
| LRRRC14B LRRQ1      | MAN1B1 MAPT7 MBOAT7 MRAP MTMR2                  |
| MGAT5S NOP58 NR2F6  | NWD1 PLEC PHC3 PHLPP2 POM121L12                 |
| PPFIA4 PRL PRK RAB15 | RBPJ RPM12B RSPH9 BRM752 SCAPER SEC22A         |
| Protein | Description |
|---------|-------------|
| SENP7, SIPA1L2, SLC22A15, SLC26A9, SLC40A1, SMTLN1, SNAI1, SNTG1, STAC3, TABC1, TAS2R20, TCHH, TMEM63A, TMEM143, TMG2D, TM4SF4, TAS2R31, TRIM33, TROAP, TYK2, SPC25, THADA, UPF2, UBR3, UMODL1, XPO5, ZFP2, ZNF219, ZFP1, ZNF391, | Rubella: no filter |
| DRD4, GRIK2, GRIK3, GRIK4, GRIK5, | Cholinergic CHRNA3 ACHE Dopamine receptors dopaminergic receptor isoform short |
| glur7, HTR3C, GRIN2A, GRIN2B, GRIN2D, HLA-A, HLA-B, HLA-DRB1, NOS1, NRG2, NRXN1, PRODH, SHANK3, | Number of SZ |
| genes = 21, DISC1, DRD2, | 2 NMDA receptor subunit epsilon-3 NMDA receptor subunit epsilon-4 GABA GABA transporter 1 Synaptic |
| GRASP, HIPK4, SYNPO, PDZD7, SHANK1, SHANK3, SYNCRIP, DISC1, related | Neuregulin and growth act5a, NRG2, GDF1, IGFBP3, Translation initiation |
| EIF3A, E2F1, Channels Calcium CACNAB1, CACNA1E, Signalling | |
| GRB10, RASSF7, INPP1, PTPRK, PPP1R14C, | Immune cytokine |
| HLA-A, HLA-B, MDR/TAP, IL17D, Structural ACTN4, COL1A1, COL7A1, MYH14, | |
| ABTB2, ADAMTSL5, ADRA1D, AKAP5, AKNA, AIP1, ARHGDAP30, BAALC, BST1, CECR6, CHAC2, CKAP4, CTDP1, DCAF1L2, ENAH, EPN3, FARS2, FLNB, HCG4P6, HMGN1, INA, IQSEC2, ITGA8, ITGB4, KLHL4, | |
| KLHDC4, LARP1, LEMD2, MED23, MFSD6, MON1B, | |
| MRVIL, MYO1B, NCKX4A2, NSAP1, NTN1, NXF5, OPMCL, OS9, OTP1, | |
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 | HTLV1 [100] |
| 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      | 7             | Phagosome                        | 12 | Allograft rejection                   | 11 |
| infection                  |               |                                 |    |                                       |    |
| Epithelial cell signaling  | 6             | Gap junction                     | 11 | Hematopoietic cell lineage            | 11 |
| in Helicobacter pylori     |               |                                 |    |                                       |    |
| infection                  |               |                                 |    |                                       |    |
| 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             | 8  |
| Bacterial invasion of      | 3             | SNARE interactions in vesicular transport | 4  | Autoimmune thyroid disease           | 8  |
| epithelial cells           |               |                                 |    | Chemokine signaling pathway          | 8  |
| E.coli infection           | 3             |                                 |    | Leukocyte transendothelial migration  | 8  |
| RIG-I-like receptor        | 3             |                                 |    | Natural killer cell mediated          | 8  |
| signaling pathway          |               |                                 |    | cytotoxicity                          |    |
| Cytosolic DNA-sensing      | 2             |                                 |    | Adipocytokine signaling pathway       | 7  |
| pathway                    |               |                                 |    | Asthma                                | 7  |
| Shigelllosis               | 2             |                                 |    | 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  |
|                            |               |                                 |    | Lysosem                              | 2  |
|                            |               |                                 |    | Regulation of autophagy              | 2  |
|                            |               |                                 |    | Fc gamma R-mediated phagocytosis      | 1  |
|                            |               |                                 |    | Primary immunodeficiency              | 1  |

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].
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 incidence of schizophrenia and also to be of clinical particularly prior to pregnancy might be expected to reduce the incidence of schizophrenia and to pair them with the various pathogenic species and human diseases. This would greatly aid our understanding of the implication of pathogen in disease and may lead to radically new therapies and prevention strategies in many disorders.

### Table 6: Human homologues of Norwalk virus proteins.

| Dopamine metabolisers | Amine transporters | Others |
|-----------------------|--------------------|--------|
| AOC2 amine oxidases   | SLC6A2 (Noradrenaline) | CADPS2 amine release activator |
| AOC3***               | SLC6A3 (Dopamine)   | CDCA7 cell division cycle associated 7 |
| KDM1A amine oxidase demethylase | SLC18A1 vesicular monoamine | CDCA7L |
| KDM1B***              | SLC18A2***          | IL4I1 cytokine |
| MAOA monoamine oxidase| SLC22A2 organic cation | PICK1 postsynaptic scaffold |
| MAOB***               | SLC22A3 extraneuronal monoamine | |
| RNLS renalase amine oxidase | SLC29A4 (Na+/H+) | |
| SMOX spermine oxidase |                    |        |
| SPR sepiapterin reductase |                |        |
| Monoamine synthesis cofactor |            |        |
| SULT1A1 sulphotransferases |               |        |
| SULT1A3 monoamine metabolite |           |        |
| sulphation             |                    |        |
| SULT1A4                |                    |        |

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