

## Research Article

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

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Received 30 November 2010; Accepted 25 February 2011

Academic Editor: Man W. Tan

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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 burgdorferi*) 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.

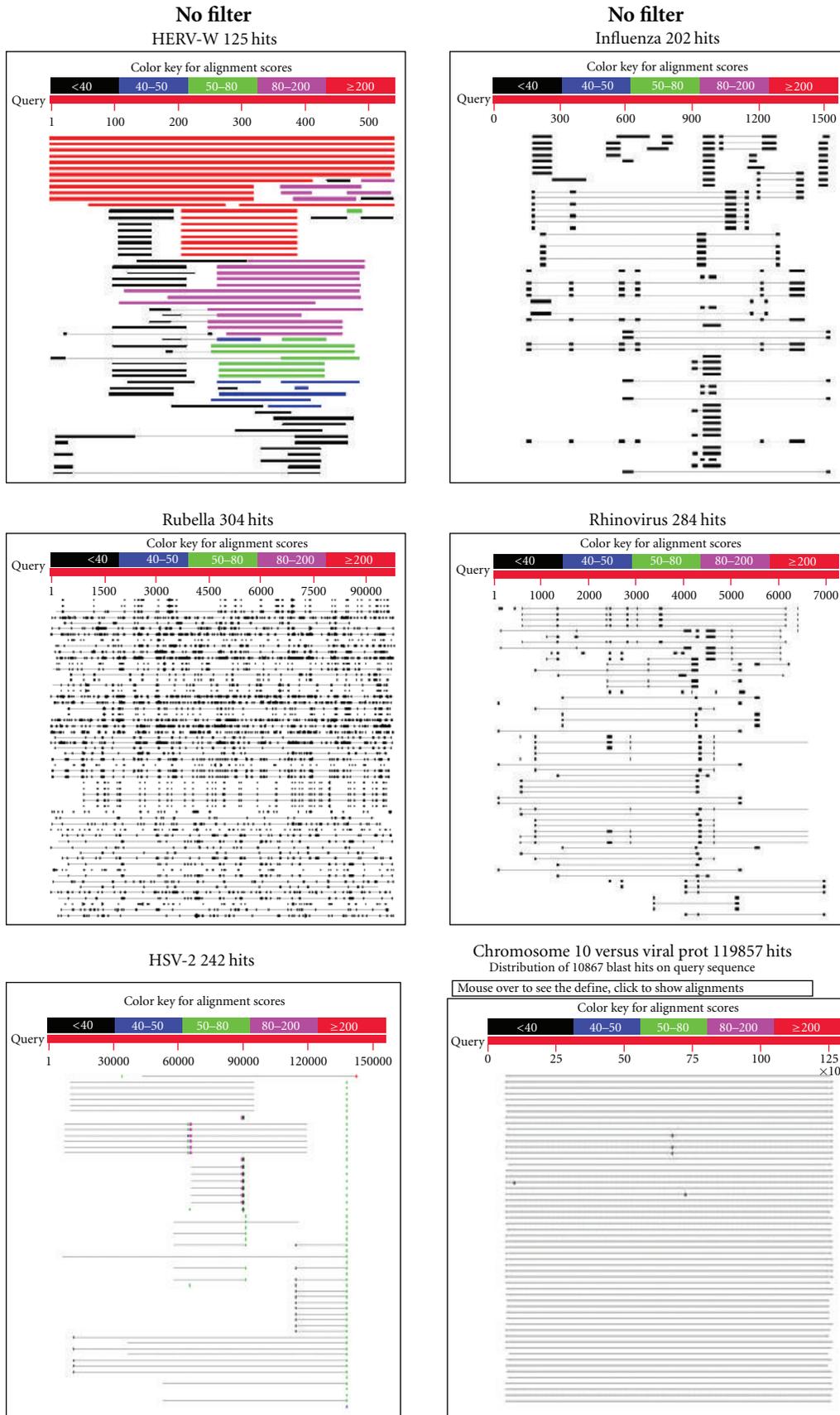


FIGURE 1: Continued.

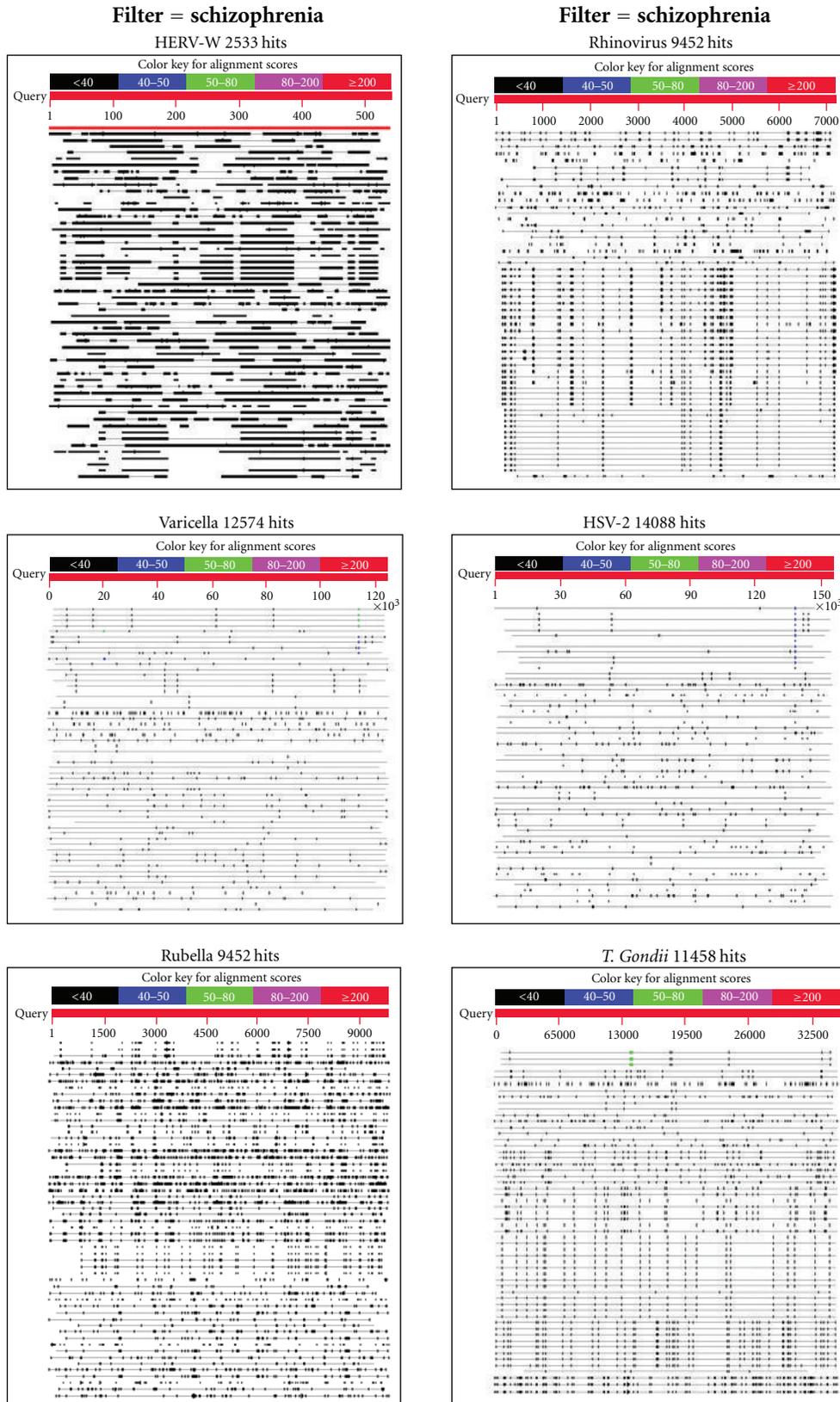


FIGURE 1: Screenshots of the pictorial representation of the viral BLAST results against the human proteome. The streaks dotted throughout the human genome/proteome represent the areas of homology, some with contiguous sequences of 5 or more amino acids. The number of hits is shown for each virus or 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.

>gi|61742823|ref|NP\_061132.2| disrupted in schizophrenia 1 protein isoform L [Homo sapiens]

**MPGGG****PQGAPAAAGGGGVSHR**<sub>AGSRDCLPPAACFR</sub>**RRRLARRP**  
**G****YM****RS****STGP**<sub>GIGFLSPA</sub>**VGTLFR****FPG****GVS****GEEES**  
**HHSES**<sub>RARQCG</sub>**DSRGLLVR****SPV****SKSAAA****PTV**<sub>TSV</sub>**RG****TS****AHFGIQLRG****GTR****LPDRLS****WPC**  
**GPGSAGW**<sub>QQEFAAMD</sub>**SSETLDASW**<sub>EAACSDGARRV</sub>**RAAGSLPSA**<sub>ELSSNSCSPG</sub>**CGPE****VP**  
**PTPP****GSHSA**<sub>FTSSFSFI</sub>**RLSLGS****AGERGEAEGCPPS****REAES****HCQSPQE**  
**MGA**<sub>KAAS</sub>**LDGP****HEDPR**<sub>CL</sub>  
**SRPFSLLATRVSADLAQ**<sub>AA</sub>**RNSSRPER**<sub>DMHSLP</sub>**DMDP****GSSSSLD**  
**PSL****AGCGG****DG****SSGSGDAH**<sub>SWDT</sub>**LLRKWE****PV****LDCLLRNR****RQ****MEVISLR**  
**LKLOKLOED****AVEN****DDYDKA**<sub>ETLQQRLEDLEQEK</sub>**SLHFQ****LPSR****QPALSSFLGHLAAQVQAALRRG**  
**A****TQ****QASGDDTHTP**<sub>LRM</sub>**EPRLLED****SLHVSIT**  
**RRDW**<sub>LLQEK</sub>**QQLQ**<sub>KEIA</sub>**LQARMFV****LEAKDQQL****RREIE****EQEQQLQWQGCDLTP****VGQSLG****QLQEVSK**  
**ALQDTLASAGQIPFHA****PPETIRSLQ****ERIKSLNLSLKE****ITTKV****MEKFCSTL****RKKVNDIETQLPALLEAKM**  
**HA****SGNHFW****TAK****DLTEE****RS****LT****S****EREGLEG****LLSKLLVLIQSLQLQEARGSLSVEDERQM****DDLEGAAPP**  
**IP****PRL****H****SE****D****K****R****K****T****P****L****K**<sub>V</sub>**LEEWKT****HLIPSLH****CA****GG****EQ****K****E****ES****Y****L****S****A****E****L****G****E****K****C****E****D****I****G****K****L****L****Y****L****E**  
**DQLHTA****I****H****S****H****DE****LI****Q****S****L****R****R****E****L****Q****M****V****K****E****T****L****Q****A****M****I****L****Q****L****Q****P****A****K****E****A****G****E****R****E****A****A****A****S****C****M****T****A****G****V****H****E****A****Q****A**

(a) Varicella virus vatches within DISC1

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

>gi|61742823|ref|NP\_061132.2| disrupted in schizophrenia 1 protein isoform L [Homo sapiens]

**MPGGG****GPQGA****PA****AAGGGGV****S****HR**<sub>AGSRDCLP</sub>**PAA****CFRRRL**  
**ARRPG****Y****M****R****S****S****T****G****P**<sub>GIGFLSPA</sub>**V****G****T****L****F****R****F****P****G****V****S****G****E****E****S****H****H****S****E****S**

(b)

FIGURE 2: Continued.

RARQCGLD **SRGLIV** RSPV **SKSAAAPTV** TSVRGT SAHFGIQLRG**GTRL** PDRLS  
**WPC** **GPGSAG** WQQEFAAMD **SSETLDASWEAAC** SDGAR**RVRAAG** SLPSAELS  
 SN **SCSPGCGPEVPP** TPPGSHSA FTSSFS **FIRLSLGS** AGE  
 RGEAE **GCPPS** REAESHCQSPQEM **GA** KAAS LDG  
**PHEDPR** CLSRPFS **LLATRV** SADLAQAA RNSSRPER DMHSLP DMD  
**PGSSSSLD** PSL AGCGGDGSSGSGDAH SWDTLLRKWEPVL  
 RD **CLLRNR** RQ **MEVI** SLRLKLQKLQED **AVENDDYDKA** ETLQORLEDLEQEKIS  
 LHFQLPSRQPALSS **FLGH** LAA QVQAA **LRRGA** TQQASGDDTHTP LRMEP  
**RLLED** SLHVS **ITRRDW** LLQEK **QQLQ** KEIEALQARMFVLEAKD **QQLR** REIEEQEQ  
**QLQW** GCDLTP **LVGQL** SLGQLQEVSKALQDTLASAGQIPFHAET **PPETIRSLQ**  
**ERIKSLNLS** LKEITTKVCMSEKFCSTLRKK **VNDI** ETQLPALLEAKMHAISGNHFWTAKDLT  
 EEIRSLTSEREGLE **GLLSK** LLVLIQSLQEQEARGSLSVEDERQM **DDLEGAAPP**  
**IP** PRLHSEDKRKTPL **KVLEEW** KTHLIPSLHCAGGEQK **EESY**  
**I** LSAELGEKCEDI **GKKLLY** LEDQLHTAIHSHDEDLIQSLRRELQMVKETLQAMILQLOPAK  
 EA **GEREAAASC** MTAGVHEAQA

KEY

HSV1 HSV-2 
 Roseophage
Human cosavirus
Hepatitis c
Influenza  
Klebsiella phage
Rubella
Enterobacteria phage  
Pseudomonas phage
Staphylococcus phage
Feline coronavirus  
Mycobacterium phage
Burkholderia Phage  
 Culex nigripalpus NPV 
 Lactococcus phage
Varicella
Chrysoideixis

(b)

FIGURE 2: Continued.

~~chalcites nucleopolyhedrovirus~~ **Acanthamoeba polyphaga**  
~~mimivirus~~ **JC Polyoma virus** **Varicella** **Staphylococcus**  
**phage** **Synechococcus phage** **Vaccinia virus** **Bornavirus** **HERV-W**

(b) Multiple virus vatches within DISC1

>gi|61742823|ref|NP\_061132.2| disrupted in schizophrenia 1 protein isoform  
 L [Homo sapiens]

**MP** **GGGP** **QG** **APAA** **AGGGGV** **SHR** AGSRDCLPPAACFRRRRLA  
 RRP**GY** **MR**<sup>r</sup> **S**<sup>r</sup> **S**<sup>r</sup> **T**<sup>r</sup> **GP** GIGFLSPAVGTLFRFP **GVSG** **EES** **HHSES** RARQCGLDSRGLL  
 VRSPV **SKS** **AA** **APT** **V** TSVRG TSAHFGIQLRGGTRLPDRLS **W** **PCGP** **S** **SAGW** QQEFA  
 AMDSSETLDASWEAACSDGARRVRAAGSLPSAELSSNSCPG **CGPE** **VPPTP** **PGSH** **SA** FT  
 SSFSFIRLSLGS **AGERGE** **AEGGP**<sup>r</sup> **P**<sup>r</sup> **S**<sup>r</sup> **R**<sup>r</sup> **E** **ESH** **CQ** **SPQE** **MGA** KAASL  
**DG**<sup>r</sup> **P**<sup>r</sup> **H**<sup>r</sup> **E** **DPR** CLSRPFLLATRVSADLAQAA **RNSS** **RPER** DMHSLP **DM** **D** **PG**  
**S**<sup>r</sup> **S**<sup>r</sup> **S**<sup>r</sup> **S**<sup>r</sup> **LD** PSL **AG** **CGGD** **G**<sup>r</sup> **S**<sup>r</sup> **S**<sup>r</sup> **r** **GS** **GD** **AH** SWDTLLRKWEPVLRDCLLRNR  
 QMEVISLRLKQLQLED **A**<sup>r</sup> **V**<sup>r</sup> **E**<sup>r</sup> **N**<sup>r</sup> **DD** **YDKA** ETLQQRLEDLEQEKISLHFQL **PSR** **QP** **ALSS** **FLGH** **LA**  
 AQVQAALRRGA **TQQA** **SGDD** **THTP** LRMEPRLLED **SLHVSITRRDWLLQEK** **QQLQ** KEIEA  
 LQARMFVLEAKDQQLRREIEEQEQQLQWQGCDLTPLVGQLSLQQLQEVSKALQDTLASAGQIPFHA**E** **PPE**  
**TIR** **S** **LQ** ERIKSLNLSLKEITTKVMEKFCSTLRKKVNDIETQLPALLEAKMHAISGNHFWTAKDLTEEIRSLTSE  
 REGLEGLLSKLLVLIQSLQEQARGSLSVEDERQM **DDLEG** **AA** **PP** **PP** **PP** **RLHS** **EDKR**  
**KTPLK** VLEEWKTHLIPSLHCAGGEQK **EESYI** LSAELGEKCEDIGKLLYLEDQLHTAIHSHDEDLIQSLR

(c)

FIGURE 2: Continued.

RELQMVKETLQAMILQLQPAKEA **GERE** **AAAS** CMTAGVHEAQA

## Key

**Influenza** Influenza **Influenza** **HSV-2** ~~HSV-2~~ **HSV-2**

Rubella Rubella ~~Varicella~~ **Rhinovirus**<sup>r</sup>

(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 Burgdorferri (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](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/gvnn/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 if 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

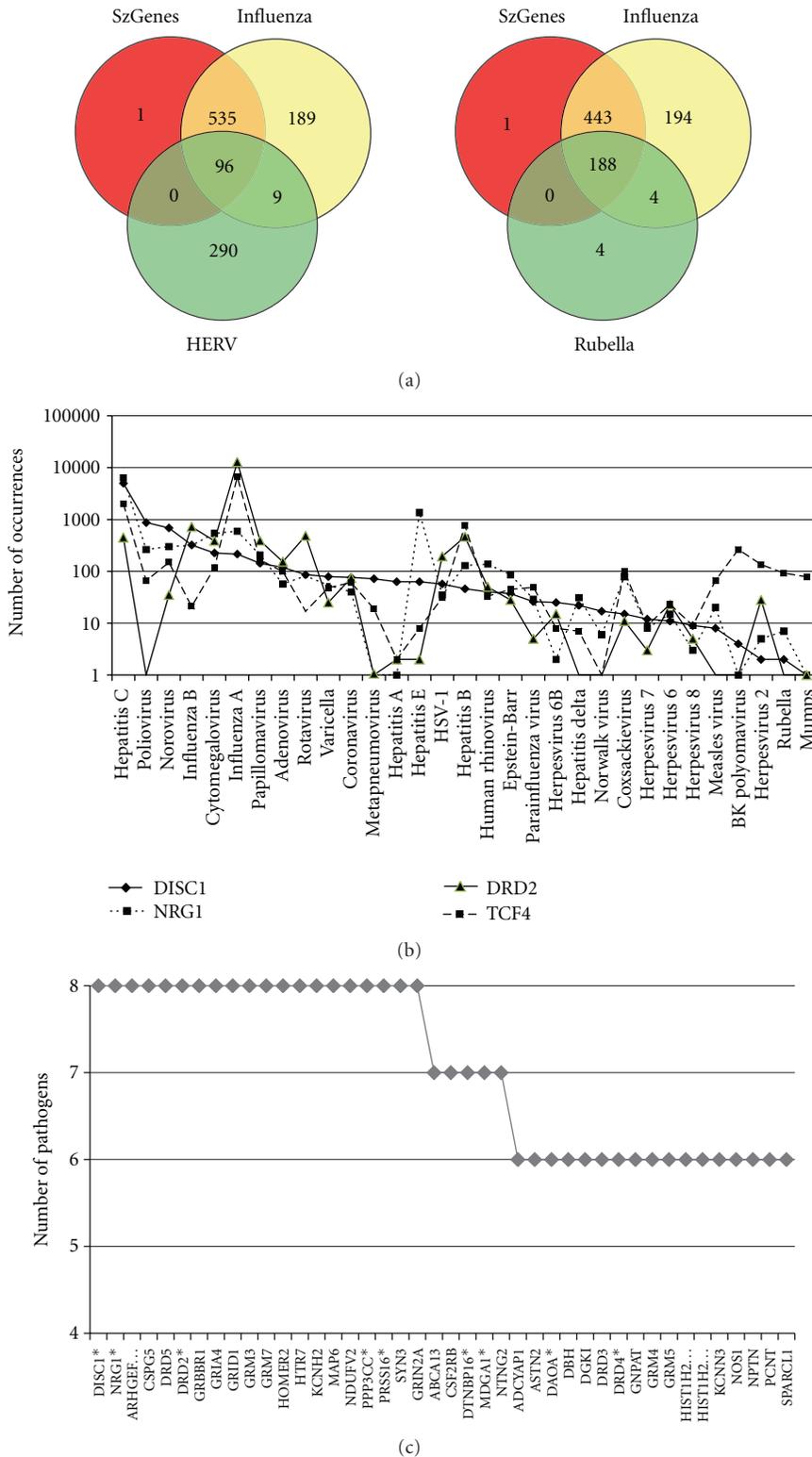


FIGURE 3: (a) Venn diagrams of the number of Schizophrenia gene products ( $N = 632$ ) with homology to the rubella, HERV-W and influenza viruses. The singleton in SZ-genes was different on each occasion: Thus, all genes are covered. (b) The viral matching spectra of DISC1, neuregulin, the dopamine D2 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/>.

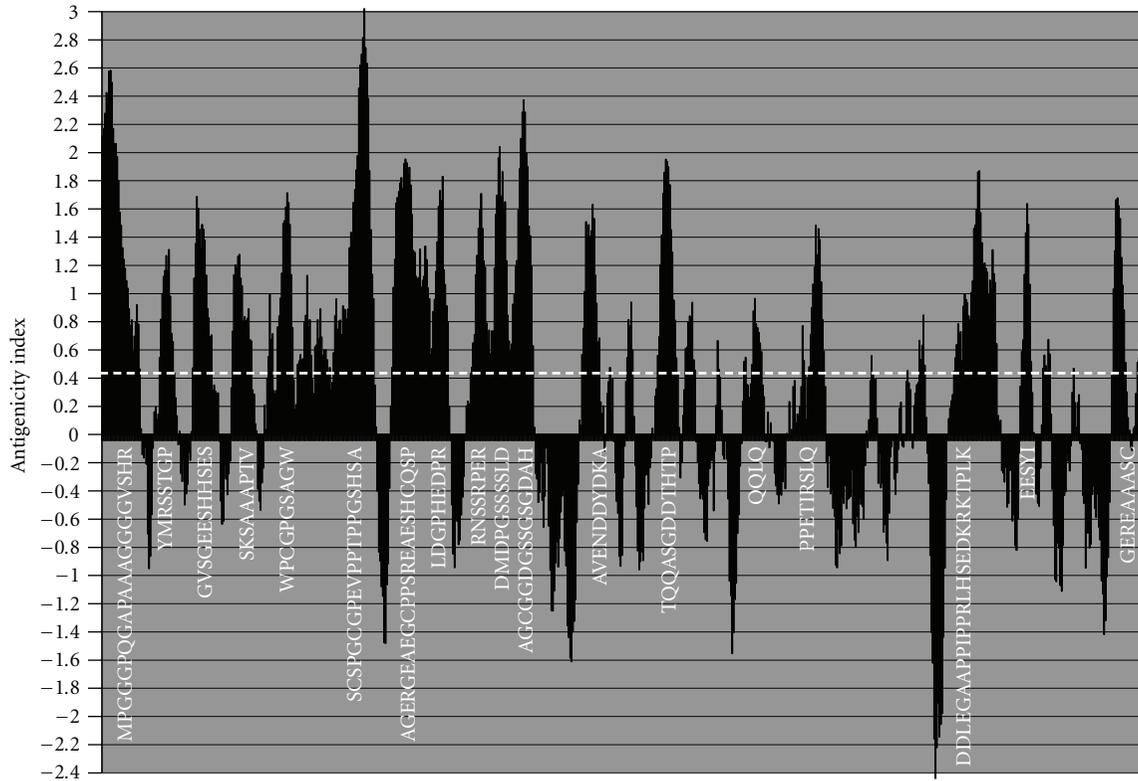


FIGURE 4: The antigenicity (B-cell epitope prediction) of DISC1: the amino acid sequences with an index of  $>0.35$  are considered as epitopes. A value of 0.8 was chosen to define highly antigenic regions as seen in Figure 2. The amino acid sequences of these highly antigenic regions are shown.

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 thalamo-cortical 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

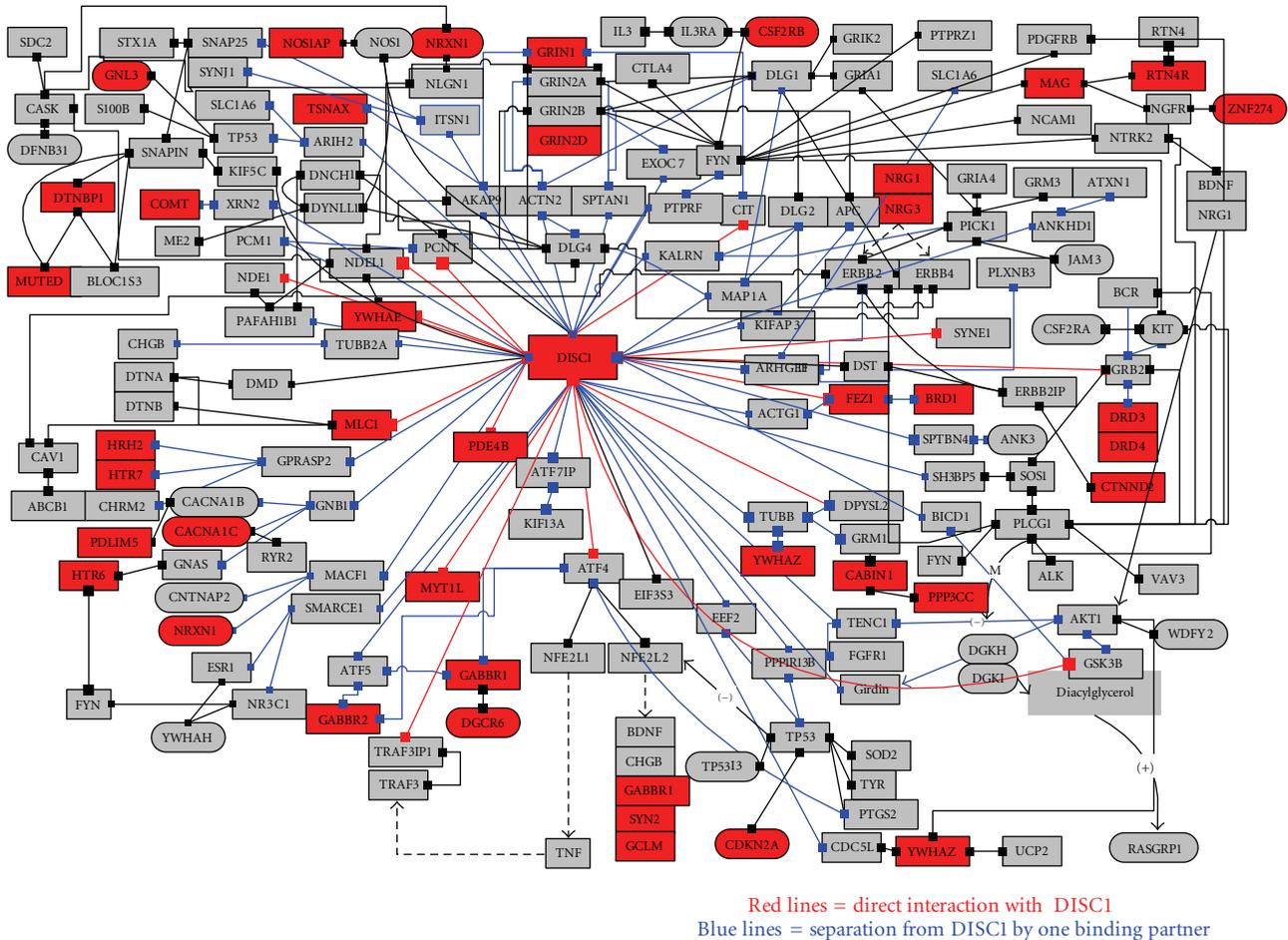


FIGURE 5: The DISC1 interactome see <http://www.polygenicpathways.co.uk/discforum.htm>. Proteins in red are homologous to Rubella proteins.

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 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].

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

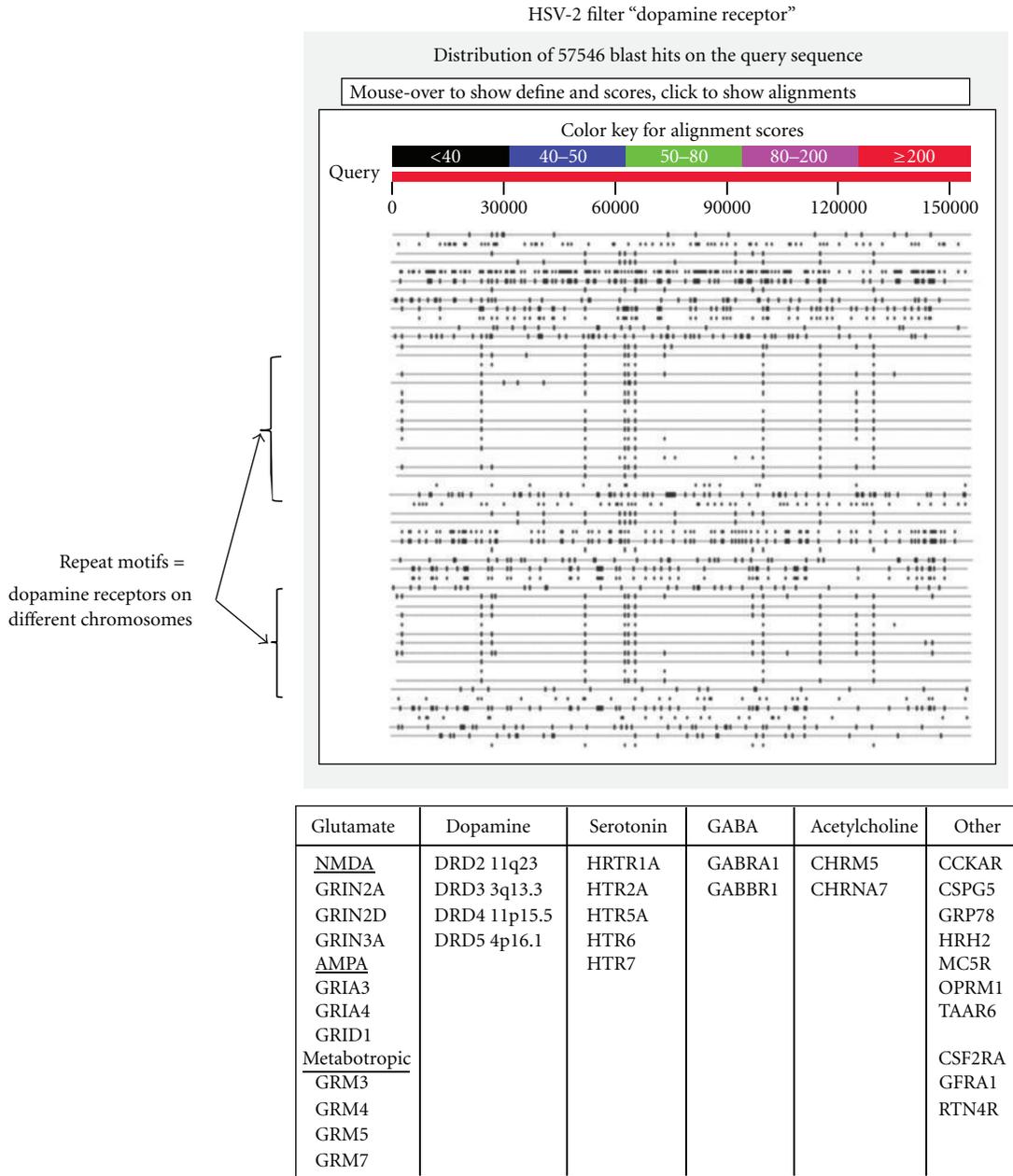


FIGURE 6: A screen shot of the HSV-2 BLAST results using the filter “dopamine receptor”. The repeated patterns correspond to dopamine receptors on different chromosomes as shown in Table 1. Homology with glutamate, serotonin, GABA, acetylcholine and other receptors is also noted.

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

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 <b>ALDH1A2</b> <sub>COMT</sub> <b>DDC</b> <b>DRD2</b> <b>DRD5</b>
Filter	<b>SLC18A2</b> <b>TH</b> Serotonin related <b>HTR1A</b> <b>HTR2A</b> <b>HTR3A</b> <b>HTR3B</b>
“schizophrenia”	<b>HTR3E</b> <b>HTR5A</b> <sub>HTR7</sub> Glutamate related <b>DAO</b> <b>GRIA2</b> <sub>GRIA3</sub>
Number of SZ	<b>GRIA4</b> <b>GRID1</b> <b>GRIN2A</b> <b>GRIN2D</b> <b>GRIN3A</b> <b>GRIK3</b> <sub>GRIK5 GRM2</sub>
genes = 103	<b>GRM3</b> <b>GRM7</b> Synaptic <sub>CABIN1 CPLX2 DTNBP1</sub> <b>DRP2</b> <b>GRIP1</b>
ACSM1 AHI1 ALDH1A2 ANK3	<b>RPGRIP1L</b> <sub>HOMER1</sub> <b>HOMER2</b> <b>HOMER3</b> <b>HIPK3</b> <sub>SPTAN1</sub>
ARHGAP18 ARHGEF10 ARVCF	<b>SYN2</b> <sub>SYN3</sub> <b>RGS9</b> <b>SNX6</b> GABA related <b>GABRB1</b> <b>GABRG1</b>
ASTN1 BRD1 CACNG2 CHRFBAM7A	<b>GABBR1</b> Cholinergic <sub>CHRFBAM7A</sub> <b>DISC1</b> related <b>ATF7IP</b>
CIT CLINT1 COMT CPLX2 CSF2RB	<b>DISC1</b> <b>FEZ1</b> <b>MLC1</b> <b>PCM1</b> <b>PCNT</b> Myelin related <sub>MBP</sub> <b>MOG</b>
CSPG5 CTNND2 DAO DGKI DISC1	<b>MPZL1</b> <sub>NOTCH4</sub> Translation initiation <b>EIF3D</b> <sub>EIF4A2</sub>
DRD2 DRD3 DRD5 DTNBP1 EGR4	Neuregulin and growth <b>EGR4</b> <b>GFRA1</b> <sub>CSF2RB</sub> <b>GFRA3</b> <b>NRXN1</b>
FEZ1 GABBR1 GFRA1 GFRA3	<b>NLGN4X</b> <sub>RET</sub> <b>UTRN</b> Oxidative stress <sub>NDUFV2</sub> <b>ATP2A2</b> <b>CBR1</b>
GNPAT GPC1 GPR85 GRIA3 GRIA4	<b>NDUFS1</b> Channels Calcium <b>CACNA1B</b> <b>CACNG2</b> Sodium
GRID1 GRIK3 GRIN2A GRIN2D	<b>NALCN</b> Potassium <b>KCNH2</b> <sub>KCNH7 KCNH6</sub> <b>KCNN2</b> Immune/cytokine <sub>LIF</sub>
GRM3 GRM4 GRM7 HDAC4 HIPK3	<b>TPI1</b> Structural <sub>MAP1A MAPT MYO1D</sub> <b>MAP1B</b> <b>TBCB</b> <sub>TUBB2A</sub> Signalling
HIST1H2AG HIST1H2AH HLA-DRB1	<b>DGKI</b> <b>GNB1</b> <b>IMMT</b> <b>PDE10A</b> <b>PIK3C2G</b> <b>PI4KA</b> <b>PAK3</b>
HOMER1 HOMER2 HTR1A HTR2A	<b>PPP3CC</b> <b>GNAI2</b> <b>RAPGEF6</b> <sub>RASF7 STK24</sub> DiGeorge <b>DGCR14</b>
HTR5A HTR7 IMPA2 JARID2	<b>ABCA7</b> <b>ADAM28</b> <b>AHI1</b> <sub>ANK2</sub> <b>ANK3</b> <b>ANKHD1</b> <b>APOL4</b> <b>APP</b>
KCNH2 LIF MAP6 MAPT MCHR1	
MCTP2 MDGA1 MEGF10 MLC1	
MOG MPZL1 MUTED NALCN	
NDUFV2 NEUROG1 NOS1 NOTCH4	
NRG1 NRG3 NRXN1 NTNG2 PCMI	
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	

TABLE 3: Continued.

	<p>AP3B2 ASTN1 <small>BACE1</small> <b>BRPF3</b> BRD1 CARTPT CEP63 CLDN10</p> <p>CLINT1 <b>CTNND2</b> CYFIP1 CYP26B1 <b>DCDC2</b> DKK1</p> <p>DLD <b>DNAJC6</b> DOCK9 DZIP1 <small>FNIP1</small> GDA <b>GNPAT</b> <small>GPC1</small></p> <p>GPR125 HDAC4 HDAC10 <small>HNTPNU HIST1H2AH</small> <b>HSPD1</b></p> <p>JARID2 KIF13A <b>LAMB2</b> LANCL2 LSAMP</p> <p>MCHR1<b>MDGA1</b> MCTP2 MTIF3 MUTED NC5C NBEAL2</p> <p>PAFAH1B1 PAICS PCDHA1 PCDH11Y PLXNA2 <small>PNP0</small> PRSS16</p> <p>PTGFRN <small>RAI1</small> RSRC1 SEL1L3SEMA3A <b>SIGMAR1</b> SIRPB1</p> <p>SLC25A3(PO<sub>4</sub>) SLCO3A1(anion) SP4 <small>STAB1</small> ST6GAL2 <b>STRN</b> SULT4A1</p> <p><b>TAAR6</b> <small>DK1</small> <b>TKT</b> <b>TMTC4</b> TPM1 UCHL1 UGGT2 WDR1 <small>NRG1 NFL3 ACSM1</small></p> <p>SPRY4 <small>NCOA7</small> ST8SIA2 <b>YWHAH</b> <b>ZBT20</b> <small>ZNF184</small> <b>ZNF804A</b> <small>OMG VGF MEGF10 ERWE1 PDE7B</small></p> <p>HIST1H2AG TMEM200C <small>CIT IMPA2 ATCAY LRRMT1 OLFM1 CELSR1 ABCA13 ARVCF CCDC141 ERM6 PRKCG ADAMTS4 ARHGAP18</small></p> <p>NRCAM NOVA1 <small>COX1 DRD3</small> <b>GPR85</b> <small>GRK1 KCNG5 CNTN4 GNB2 OPHN1 RELN HNRNPA2B1 INA ALDH1A3 VAMP2</small></p> <p><small>KIF21A(4) LBA2 CSPG5</small></p>
HSV-2	Dopamine related <small>COMT</small> <b>DDC</b> <b>DRD1</b> <b>DRD3</b> <b>DRD4</b> <b>DRD5</b> <b>TH</b> <b>PEMT</b>
Filter	Serotonin related <small>HTR2A</small> <b>HTR6</b> <b>HTR7</b> <b>HTR5A</b> Glutamate related <small>DAO DAOA GRIA4</small>
“schizophrenia”	<small>SLC1A4(GLUT)</small> <b>GRID1</b> <small>GRIN2D GRIN3A GRM3</small> <b>GRM4</b> <small>PRODH</small>
Number of SZ genes = 166	<b>SLC17A1</b> <b>SLC17A7(PO4/glu)</b> <b>SLC1A3(GLUT)</b> <small>KMO</small> <b>GABA – related</b> <small>GABRA1</small> <b>GABBR1</b> Synaptic <b>DLG4</b> <b>DTNBP1</b> <small>HOMER1</small> <b>HOMER2</b> <small>NOS1AP</small>
ABCA13 ACSL6 ADAM12 ADCYAP1 ADSS AHI1 ALDH1A2 ALDH3B1 ALK ANK3 ARHGAP18 ARVCF ASTN1 ASTN2 ATP6 BRD1	<b>SYN2</b> <b>SYNGAP1</b> <b>SYT11</b> <small>RGS4</small> <b>DISC1</b> related <small>DISC1</small> <small>CIT</small> <b>FEZ1</b> <b>FZD3</b> <b>NDE1</b> <b>NDEL1</b> <b>PDE4B</b> <b>TSNAX</b> Neuregulin and growth <small>ALK</small> <b>EGR2</b>

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 RPGRIPL1 RTN4R SHISA5 SIRT5	<p><b>GFRA1 NRG1</b> <small>NRG3 NRXN1</small> <b>NTF3 NPTN FGF14</b> <small>CSF2RB</small> <b>NTNG</b></p> <p><b>Myelin related</b> <b>MAG</b> <small>MPZL1</small> <b>NOTCH4 RTN4R</b> <b>Oxidative stress</b> <small>GCLM</small> <b>ATP6</b></p> <p><b>ND2</b> <b>Channels Calcium</b> <b>CACNA1C</b> <b>Potassium</b> <b>KCNN3 KCNH2</b></p> <p><b>Immune/cytokine</b> <b>IL1A</b> <b>MICB</b> <small>TRAF3IP1</small> <b>Structural</b> <b>MAP4</b> <b>MAP6</b> <b>MYH9</b></p> <p><b>MYT1L</b> <b>Signalling</b> <b>ARHGAP18</b> <b>ARHFGEF10</b> <b>GNAL</b></p> <p><b>MAPK14 IMPA2</b> <b>PDE4D</b> <b>PLAA</b> <b>PLA2G4C</b> <b>PPP1R1B</b> <b>RAPGEF6</b></p> <p><b>UHMK1</b> <b>DiGeorge</b> <small>DGCR2</small> <b>DGCR6</b></p> <p><b>ABCA13</b> <b>ADAM12</b> <b>ADSS</b> <b>AHI1</b> <b>ARVCF</b> <b>BRD1</b> <b>BT2NA2</b> <b>CHN2</b></p> <p><b>CSPG5</b> <b>DLX1</b> <b>ENO2</b> <b>FBCL2</b> <b>FCYD6</b> <b>GRP78</b> <b>JARID2</b></p> <p><b>KPNA3</b> <b>NPAS3</b> <b>NUMBL</b> <b>OPRM1</b> <b>PCDH8</b> <small>PLXNA2</small> <b>PNPO</b> <b>POM121L2</b></p> <p><b>PRSS16</b> <small>GRIN2A ALDH1A2 - PCM1</small> <b>TAAR6</b> <small>VRK2 -</small> <b>TXNDC5</b> <b>1</b> <small>GNL3 HTR2C NDUFV2 FXR1 - MC5R DBH CDR2A</small></p> <p><small>NEUROG1 PADI2 CCKAR</small> <b>MLC1</b> <small>FABP7 ASIN2 CHRNA7 - - - - PPP3CC TUBA8</small> <b>PTBP2</b> <small>GRM7 TSPAN8 TPH1 HSPA12A SYN3 DKK4 - - - - - CYTB</small></p> <p><small>CCDC60 FOLDM6</small> <b>HIST1H2AH</b> <b>SLC06A1(ANION)</b> <b>MEGF10</b> <small>RPGRIPL1 - - - - - MCTP2 MDGA1 GRIA3 YWHAZ - - GNB1L SHISA5 ACSL6 GRM5</small></p> <p><b>ZNF74</b> <small>SMARCC1</small> <b>BTN3A1</b> <b>ASTN1</b> <b>TSPO</b> <b>SLC17A3</b> <small>DISC1 SYNG1 CS2RA SLC6A5(GLY) UFDL1L</small> <b>ZNF804A</b> <small>CHRM5</small></p> <p><b>YWHAZ</b> <small>MUTED SIRT5 HRH2 - SPARCL1 HTR1A CABN1</small> <b>HIST1H2BJ</b> <small>- - - - -</small></p>
<b>Influenza</b>	<b>Dopamine related</b> <b>COMT</b> <b>DRD1</b> <small>DRD3 DRD5</small> <b>Serotonin related</b> <b>HTR1A</b>
<b>Filter</b>	<small>HTR2C HTR5A HTR6</small> <b>HTR7</b> <b>TPH1</b> <b>Glutamate related</b> <b>DAO</b> <b>DAOA</b> <b>GRIA3</b>
<b>“schizophrenia”</b>	<b>GRIA4</b> <small>GRIN2A</small> <b>GRIN2D</b> <b>GRIN3A</b> <b>GRM5</b> <b>KMO</b> <b>SRR</b> <b>SLC6A5(GLY)</b> <b>SLC17A7(P04)</b>
<b>Number of SZ</b>	<b>SLC17A1</b> <small>SLC17A3</small> <b>GABA -related</b> <b>GABRA1</b> <b>GABBR1</b> <b>GABRP</b> <b>Synaptic</b>
<b>genes = 167</b>	<small>ABCA13</small> <b>DTNBP1</b> <b>DLG4</b> <b>HOMER1</b> <b>RPGRIPL1</b> <b>SYN2</b> <b>SYN3</b>

TABLE 3: Continued.

ACSL6 ADAM12 ADCYAP1	<b>SYNGAP1</b> <sup>SYNGR1</sup> <b>SYT11</b> <b>DISC1</b> related <sup>DISC1</sup> <b>CIT</b> <b>NDE1</b> <b>PCMI</b> <sup>PDE4B</sup>
ADSS AHI1 ALDH1A2	
ALDH3B1 ALK ANK3	<b>MLC1</b> <sup>TSNAX</sup> <b>Neuregulin and growth</b> <b>ALK</b> <b>NRG1</b> <b>CSF2RB</b> <b>GFRA1</b>
ARHGAP18 ARVCF ASTN1	
ASTN2 ATP6 BRD1 BTN3A1	
CCDC60 CCKAR CDKN2A	<b>NEUROG1</b> <b>CSF2RA</b> <b>EGR2</b> <b>NTNG1</b> <b>NTF3</b> <b>Myelin related</b> <sup>MAG</sup>
CHN2 CHRM5 CHRNA7 CIT	
COMT CSF2RA CSF2RB	<sup>NOTCH4</sup> <b>MPZL1</b> <b>RTN4R</b> <b>Cholinergic</b> <b>CHRM5</b> <sup>CHRNA7</sup> <b>Oxidative stress</b>
CSPG5 CYTB DAO DAOA	
DBH DGCR2 DGCR6 DISC1	<b>CYTB</b> <b>GCLM</b> <b>Channels Calcium</b> <sup>CACNA1C</sup> <b>Potassium</b> <b>KCNN3</b> <b>KCNH2</b>
DKK4 DLG4 DLX1 DRD2	
DRD3 DRD4 DRD5 DTNBP1	
EGR2 ENO2 FABP7 FEZ1	<b>Immune/Cytokine</b> <b>IL1A</b> <b>TRAF3IP1</b> <b>Structural</b> <sup>MAP6</sup> <sup>MYT1L</sup> <b>Signalling</b>
FGF14 FXR1 FZD3 GABBR1	
GABRA1 GABRP GCLM	<b>ARHFGF10</b> <sup>GNL3</sup> <sup>MAPK14</sup> <b>PLA2G4C</b> <b>PPP3CC</b> <b>UHMK1</b> <b>DiGeorge</b> ..
GFRA1 GNAL GNB1L GNL3	
GRIA3 GRIA4 GRID1 GRIN2A	<b>DGCR2</b> <b>DKK4</b> .. <b>YWHAE</b> <b>ZDHC8</b> <b>SPARCL1</b> <b>MC5R</b> <sup>POM121L2</sup> <sup>CABIN1</sup> <sup>PRODH</sup> <sup>ASTN1</sup> <sup>FZD3</sup> .. .. <sup>HSPA12A</sup>
GRIN2D GRM3 GRM4 GRM5	
GRM7 HIST1H2AG	<b>ALDH3B1</b> <b>ARVCF</b> .. <sup>UFD1L</sup> .. <sup>PPP1R1B</sup> .. <b>SIRT5</b> <sup>DRD2</sup> <b>SLC06A1(ANION)</b> .. <b>MCTP2</b> <sup>ATP6</sup> <sup>NPTN</sup>
HIST1H2AH HIST1H2BJ	
HOMER1 HOMER2 HSPA12A	<sup>MUTED</sup> <b>FBCL21</b> <sup>JARID2</sup> <sup>NDUFV2</sup> <b>PCDH8</b> .. <sup>MEGF10</sup> .. <sup>SHISA5</sup> <sup>NDEL1</sup> <b>PLXNA2</b> <sup>TSPO</sup> <b>CSPG5</b> .. <sup>TXNDC5</sup> <sup>ALDH1A2</sup>
HTR1A HTR2A HTR2C HTR5A	
HTR6 HTR7 IL1A IMPA2	<b>CHN2</b> .. <b>NPAS3</b> <sup>PCYD6</sup> .. <sup>DLX1</sup> <sup>MASH</sup> <sup>PLAA</sup> .. <b>FXR1</b> <sup>SP4</sup> <sup>GRM3</sup> <sup>GRD1</sup> .. <sup>ENO2</sup> <sup>PTBP2</sup> <sup>TH</sup> <b>TSPAN8</b>
JARID2 KCNH2 KCNN3 KMO	
MAG MAP4 MAP6 MAPK14	
MC5R MCTP2 MDGA1	<sup>PEMT</sup> <sup>RGS4</sup> .. <b>MDGA1</b> <b>AHI1</b> <sup>CCDC30</sup> <sup>SNAP29</sup> <sup>DDC</sup> <b>ZNF804A</b> <b>ASTN2</b> <sup>GRM4</sup> <sup>CCKAR</sup> <sup>RAPGEF6</sup>
MEGF10 MICB MLC1 MPZL1	
MUTED MYH9 MYT1L ND2	
NDE1 NDEL1 NDUFV2	<b>NUMBL</b> .. .. <b>SMARCC1</b> <b>ZNF74</b> .. <sup>BRD1</sup> .. <b>KPNA3</b> <b>BTN3A1</b> <sup>GRM7</sup>
NEUROG1 NOS1AP NOTCH4	
NPAS3 NPTN NRG1 NRG3	
NRXN1 NTF3 NTNG1 NUMBL	<b>HIST1H2AG</b> <sup>FGF14</sup> <b>HIST1H2AH</b> <b>FABP7</b> .. .. <sup>MYH9</sup> <sup>PDE4D</sup> <b>HRH2</b> <b>ACSL6</b> <sup>ADAM12</sup> <b>HIST1H2BJ</b> <b>MICB</b>
OPRM1 PADI2 PCM1 PDE4B	<b>ADSS</b> <sup>PNPO</sup> <b>ARHGAP18</b> .. <b>ABCA13</b> <b>YWHAZ</b> <b>TAAR6</b> <b>ADCYAP1</b> <b>GRP78</b> <b>PADI2</b>
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	
TPH1 TRAF3IP1 TSNAX	
TSPAN8 TUBA8 TXNDC5	
UFD1L UHMK1 VRK2	
YWHAE ZDHC8 ZNF74	
ZNF804A	

TABLE 3: Continued.

Rhinovirus	Dopamine related <b>DBH</b> <b>COMT</b> <b>DRD1</b> <b>DRD2</b> <b>DRD3</b> <sub>DRD5</sub> <b>TH</b> <b>SLC18A2</b>
Filter	Serotonin related <b>HTR1A</b> <b>HTR2C</b> <b>HTR6</b> <b>HTR7</b> <b>TDO2</b> Glutamate related
“schizophrenia”	<b>DAO</b> <b>DAOA</b> <b>GRIN1</b> <b>GRIN2A</b> <b>GRIK3</b> <b>GRM4</b> <b>GRM5</b> <b>GRM7</b> <b>SLC1A3(GLUT)</b>
Number of SZ genes = 176	<b>SLC1A4(GLUT)</b> <b>SLC17A3</b> <b>SLC17A7(PO4/glut)</b> <b>GABA – related</b> <b>GABRA1</b> <b>GABRB2</b> <b>GABBR1</b> Synaptic <b>HOMER1</b> <b>HOMER2</b>
ABCA13 ACSL6 ADAM12	<b>RPGRIP1L</b> <b>NOS1</b> <b>NOS1AP</b> <b>SYNGR1</b> <b>SYT11</b> <b>RG54</b> <b>DISC1</b> related – <b>DISC2</b> <b>CIT</b>
ADCYAP1 ADSS AH11	<b>FEZ1</b> <b>NDEL1</b> <b>PDE4B</b> <b>PCM1</b> <b>MLC1</b> Neuregulin and growth
ALDH3B1 ANK3 ANKK1	<b>NRG1</b> <b>NRG3</b> <b>NPTN</b> <b>CSF2RA</b> <b>EGR4</b> <b>FGF14</b> <b>GFRA3</b> <b>NRXN1</b>
APOL2 ARHGAP18	<b>NTF3</b> Myelin related <b>MAG</b> <b>NOTCH4</b> Cholinergic <b>CHRNA7</b> <b>CHRFAM7A</b>
ARHGEF10 ARVCF ASTN1	Oxidative stress <b>ALDH3B1</b> <b>ND2</b> <b>ND4</b> <b>NDUFV2</b> Channels Calcium <b>CACNA1B</b>
ASTN2 BRD1 BTN3A1	<b>CACNA1C</b> Potassium <b>KCNH2</b> Immune /Cytokine <b>LIF</b> Structural <b>MAP4</b>
C10orf120 CACNA1C CCKAR	<b>MAP6</b> signalling <b>ARHGEF10</b> <b>GNL3</b> <b>ARHGAP18</b> <b>IMPA2</b> <b>PDE7B</b> <b>PK3C2G</b>
CHI3L1 CHL1 CHRFBAM7A	<b>PPP1R1B</b> <b>RAPGEF6</b> <b>UHMK1</b> <b>PLAA</b> <b>PNPLA8</b> <b>PLA2G4C</b>
CHRM5 CHRNA7 CIT CLDN5	<b>VRK2</b> DiGeorge <b>DGCR2</b> <b>DGCR5</b> <b>DGCR6</b> ... .. <b>ABCA13</b> <b>ITIH3</b> <b>JARID2</b>
CLINT1 CLOCK CNP COMT	<b>FXR1</b> ... .. <b>PADI2</b> <b>GNB1L</b> <b>ORC3L</b> <b>SIL1</b> ... .. <b>ZNF804A</b> <b>RELN</b> ... .. <b>DKK4</b> <b>ADCYAP1</b> <b>POM121L2</b>
CSF2RA CSF2RB CTLA4	<b>ADSS</b> ... .. <b>HSPA12A</b> ... .. <b>PPP3CC</b> ... .. <b>MYH9</b> <b>INTS6</b> <b>SP4</b> <b>ESR1</b> <b>PB1</b> <b>TMEM108</b> ... .. <b>PFN4</b>
CTNND2 DAO DAOA DBH	<b>CHL1</b> <b>AK1</b> ... .. <b>CLOCK</b> <b>PNPO</b> <b>SPARCL1</b> ... .. <b>OPCML</b> <b>ZDHC8</b> <b>NUMBL</b> ... .. <b>SYN3</b>
DGCR2 DGCR5 DGCR6 DGKI	<b>PTBP2</b> ... .. <b>TSPAN8</b> ... .. <b>ST8S1A2</b> <b>ASTN1</b> <b>HIST1H2BJ</b> <b>NPAS3</b> ... .. <b>MCTP2</b>
DISC1 DKK4 DLX1 DPYSL2	<b>APOL2</b> <b>TXNDC5</b> <b>SGCR6</b> <b>CTNND2</b> <b>C10orf120</b> <b>ANK3</b> <b>HRH2</b> <b>CLINT1</b> <b>PRSS16</b>
DRD2 DRD3 DRD4 DRD5	<b>HTR2A</b> <b>MRCL3</b> <b>MRLC2</b> <b>DLX1</b> ... .. <b>GLRA2</b> <b>MICB</b> <b>PCQAP</b> ... .. <b>CLDN5</b>
EGR4 ENO2 ESR1 FABP7	<b>CHI3L1</b> <b>BRD1</b> ... .. <b>DPYSL2</b> <b>ENO2</b> <b>GNPAT</b> <b>SULT4A1</b> <b>ABCA1</b> <b>MCHR1</b> <b>TAAR6</b> ...
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 NOS1 NOS1AP NOTCH4	
NPAS3 NPTN NRG1 NRG3	
NRXN1 NTF3 NUMBL OPCML	
OPRM1 PADI2 PCM1 PCQAP	
PDE4B PDE7B PDLIM5 PFN4	
PLA2G4C PLAA PNPLA8	

TABLE 3: Continued.

PNPO POM121L2 PPP1R1B	
PPP3CC PRODH PRSS16	... BTN3A1 <b>ANKK1 MACF1 SHISA5 MDGA1</b> <small>PRODH ...</small> <b>ZBED4</b> <small>CTLA4 ZNF184</small>
PTBP2 RAPGEF6 RELN RGS4	
RPGRIPL SHISA5 SIL1 SIRT5	... <b>SIRT5</b> ...
SLC17A3 SLC17A7 SLC18A2	
SLC1A3 SLC1A4 SLC1A6	
SLC6A5 SMARCC1 SP4	
SPARCL1 SULT4A1 SYN2	
SYN3 SYNGR1 SYTI1 TAAR6	
TDO2 TH TMEM108 TSPAN8	
TXNDC5 UHMK1 VRK2	
ZBED4 ZNF184 ZNF804A	
<b>Rubella</b>	<b>Dopamine related COMT DBH DRD3 DRD4 DRD5 PEMT</b>
<b>Filter</b>	<b>Serotonin related HTR1A HTR2A HTR2C HTR5A HTR7 TPH1</b> <b>Glutamate</b>
<b>“schizophrenia”</b>	<b>related DAO DAOA GRIA3 GRIA4 GRID1 GRIN1 GRIN2A</b>
<b>Number of SZ</b>	<b>GRM3 GRM4 GRM5 GRM7 KMO</b> <small>SLC1A4(GLUT) SLC17A3</small> <b>GABA –</b>
<b>genes = 179</b>	<b>related GABRA1 GABBR1 GABRB2 GABRP</b> <b>Cholinergic</b> <small>CHRM5</small> <b>Synaptic</b>
ADAM12 ADCYAP1 ADSS	
AH11 ALDH1A2 ALDH3B1	
ANK3 ARHGAP18 ARHGEF10	<b>CABIN1 DTNBP1 NOS1AP</b> <b>RPGRIPL SNAP29 SYN2 SYN3 RGS4</b>
ARVCF ASTN1 ASTN2 ATP6	
BDNF BRD1 BTN2A2	<b>SYNGAP1 SYNGR1 SYTI1 DISC1</b> <b>related DISC1 PCMI PDE4B NDEL1</b>
CACNA1C CCDC60 CCKAR	
CDKN2A CHN2 CHRM5	
CHRNA7 CLOCK COMT	<b>FEZ1 FZD3</b> <b>Neuregulin and growth NRG1 ERBB1 ERBB3</b>
CSF2RA CSF2RB CSPG5	
CYTB DAO DAOA DBH	<b>ERBB4 GFRA1 NTF3 NTNG1 FGF14</b> <b>Myelin related NOTCH4 RTN4R</b>
DGCR2 DGCR6 DISC1 DKK4	
DRD2 DRD3 DRD4 DRD5	<b>QK1</b> <b>Oxidative stress</b> <b>CYTB</b> <small>GCLM ND2</small> <b>NDUFV2</b> <b>Channels Calcium</b>
DTNBP1 EGR2 ENO2 ERBB2	
ERBB3 ERBB4 FABP7 FBXL21	
FEZ1 FGF14 FXR1 FXYD6	<b>Potassium KCNN3 KPNA3</b> <b>Immune/cytokine IL1A</b> <b>TRAF3IP1</b> <b>Structural</b>
FZD3 GABBR1 GABRA1	
GABRB2 GABRP GCLM	<b>MAP6</b> <small>MYTIL</small> <b>Signalling</b> <b>ADCYAP1 AK1 ARHGEF10 CDKN2A GNAL</b>
GFRA1 GNAL GNB1L GNL3	
GPC1 GRIA3 GRIA4 GRID1	<b>GNB1L</b> <small>GNL3 MAPK14 IMPA2 PLAA PLA3G4C REPGEF6</small> <b>PDE4D PPP1R1B</b>
GRIK3 GRIN1 GRIN2A	
GRIN2D GRM3 GRM4 GRM5	
GRM7 HIST1H2AG	<b>DiGeorge</b> <b>DGCR2 DGCR6</b> ... <small>ERBB2 MEGF10 NDE1 HIST1H2A2A</small> <b>TXNDC5 ASCL6</b> <small>SHISA5 ZNF804A</small>
HIST1H2AH HIST1H2BJ HLA-	
DRB1 HOMER1 HOMER2	
HTR1A HTR2A HTR2C HTR5A	<b>JARID2 FXYD6 BTN2A2</b> ... <small>FBXL21 NRXN1 ... CHRNA7</small> <b>NUMBL</b> <b>ARVCF</b> <small>HTR6 ALDH1A2 ... SPARCL1</small>

TABLE 3: Continued.

HTR6 HTR7 IL1A IMPA2	TSPO <b>CCDC60</b> YWHAE <small>KCNH2 DKO1 MLC1</small> <b>CSPG5</b> PLXNA2 <b>MCTP2</b> GPC1 <small>VRK2</small>
JARID2 KCNH2 KCNN3 KMO	
KPNA3 KREMEN1 MAG	<b>CCKAR</b> ASTN2 <small>DMDC1 SLC18A3 SLC18A4 SLC18A5 SLC18A6 SLC18A7 SLC18A8 SLC18A9 SLC18A10 SLC18A11 SLC18A12 SLC18A13 SLC18A14 SLC18A15 SLC18A16 SLC18A17 SLC18A18 SLC18A19 SLC18A20 SLC18A21 SLC18A22 SLC18A23 SLC18A24 SLC18A25 SLC18A26 SLC18A27 SLC18A28 SLC18A29 SLC18A30 SLC18A31 SLC18A32 SLC18A33 SLC18A34 SLC18A35 SLC18A36 SLC18A37 SLC18A38 SLC18A39 SLC18A40 SLC18A41 SLC18A42 SLC18A43 SLC18A44 SLC18A45 SLC18A46 SLC18A47 SLC18A48 SLC18A49 SLC18A50 SLC18A51 SLC18A52 SLC18A53 SLC18A54 SLC18A55 SLC18A56 SLC18A57 SLC18A58 SLC18A59 SLC18A60 SLC18A61 SLC18A62 SLC18A63 SLC18A64 SLC18A65 SLC18A66 SLC18A67 SLC18A68 SLC18A69 SLC18A70 SLC18A71 SLC18A72 SLC18A73 SLC18A74 SLC18A75 SLC18A76 SLC18A77 SLC18A78 SLC18A79 SLC18A80 SLC18A81 SLC18A82 SLC18A83 SLC18A84 SLC18A85 SLC18A86 SLC18A87 SLC18A88 SLC18A89 SLC18A90 SLC18A91 SLC18A92 SLC18A93 SLC18A94 SLC18A95 SLC18A96 SLC18A97 SLC18A98 SLC18A99 SLC18A100</small> <b>FXR1</b> ASTN1 <small>GRIN2D MICB PTBP2 SRR NRG3 EGR2 MPZL1 CSF2RA SMARCC1 HNF1B</small>
MAP4 MAP6 MAPK14 MC5R	TH HRH2 <b>ADAM12</b> <small>PCDH8 MAG</small> <b>ZNF74</b> <b>YWHAZ</b> <small>ATP6 ANK3</small> <b>TSPAN8</b>
MCTP2 MDGA1 MEGF10	
MICB MLC1 MPZL1 MUTED	
MYH9 MYT1L ND2 NDE1	
NDEL1 NDUFV2 NEUROG1	<b>PER1</b> <b>TUBA8</b> ARHGAP18 <small>NRGN MYH9</small> <b>ENO2</b> <small>SIRT5</small> <b>BRD1</b> HOMER2 <b>GRP78</b>
NOS1 NOS1AP NOTCH4	
NPAS3 NPTN NRG1 NRG3	
NRGN NRXN1 NTF3 NTNG1	<b>TAAR6</b> <small>HIST1H2BJ KREMEN1</small> <b>SLCO6A1</b> <b>HIST1H2AH</b> <small>CLOCK PRSS16 PADI2</small>
NTNG2 NUMBL OPRM1	
PADI2 PCM1 PDE4B PDE4D	
PDLIM5 PENT PLAA PLXNA2	<b>PDLIM5</b> <b>MDGA1</b> <small>CACNA1C ADSS ZDHHC8</small> <b>AHI1</b> <small>OPRM1 UFD1L</small> <b>NPAS3</b>
POM121L2 PPP1R1B PPP3CC	
PRODH PRSS16 PTBP2 QK1	<b>MC5R</b> <small>POM121L2</small> <b>DKK4</b>
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	
Varicella	Dopamine related <b>COMT</b> <b>DDC</b> <b>DRD2</b> <b>DRD5</b> Serotonin related
Filter	<b>HTR2C</b> <small>HTR7</small> <b>HTR3A</b> <b>HTR3D</b> <b>TPH2</b> <small>TPH1</small> Glutamate related <b>GRIN1</b>
“schizophrenia”	<small>GRIN3A</small> <b>GRIN2A</b> <b>GRIK1</b> <small>GRIK5 GRM2 GRM7</small> <b>SLC6A5(Gly)</b> <b>SLC17A6</b>
Number of SZ	<b>GABA –related</b> <b>GABRA5</b> <small>GABBR1</small> <b>Synaptic</b> <small>DLGAP2</small>
genes = 75	<b>RPGRIP1L</b> <b>NOS1AP</b> <b>RGS9</b> <b>SPTBN4</b> <b>HIPK3</b> <small>STX7 SYNGR1</small> <b>DISC1</b>
ABCA13 ACSL6 ALDH1A2	related <b>DISC1</b> <b>CIT</b> <b>FEZ1</b> <small>PCNT PCM1 PDE4B</small> <b>Neuregulin and growth</b> <small>NRG1 NRG3</small>
ANK3 ANKK1 ARHGAP18	
ASTN1 BRD1 BTN3A2	<small>NTF3</small> <b>NTNG2</b> <b>CSF2RA</b> <b>NRXN1</b> <b>EGR2</b> <small>NRXN3 NLGN4X</small>
CACNA1C CHRFA7A	
CHRM5 CHRNA7 CNTNAP2	
COMT CSPG5 CTNND2	<b>UTRN</b> <b>VGF</b> Myelin related <b>NOTCH1</b> <b>OMG</b> Cholinergic <b>CHRM5</b>
CTXN3 DAO DBH DGCR2	
DGKI DPYSL2 DRD2 DRD5	<small>CHRFA7A</small> <b>Oxidative stress</b> <b>COX2</b> <b>ND1</b> <small>ND5</small> <b>NDUFS1</b> <b>QDPR</b> <b>Channels</b>
ESR1 FZD3 GABBR1 GABRA1	

TABLE 3: Continued.

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

TABLE 3: Continued.

SZ genes = 182	
ADAM12 ADCYAP1 ADSS	<b>GRM3 GRM4</b> <small>PRODH</small> <b>KMO SLC6A5(GLY)</b> <small>SLC17A1</small> <b>GABA -related</b>
AHI1 ALDH1A2 ALDH3B1	<b>GABRP</b> <b>Synaptic</b> <small>DTNBP1</small> <b>CABIN1 HOMER1 NOS1NOS1AP</b>
ANK3 ARHGAP18 ARHGEF10	<b>SYNGAP1 SYN2 SYN3 SNAP29 SYNGR1 SYT11</b> <b>RGS4 DISC1 related</b>
ARVCF ASTN1 ASTN2 ATP6	<b>DISC1 FEZ1 FZD3 NDE1PDE4B</b> <small>TSNAX</small> <b>MLC1</b> <b>Neuregulin and growth</b>
BRD1 BTN2A2 BTN3A1	<b>ERBB2 ERBB3 EGR2 FGF14</b> <small>GFRA1</small> <b>NEUROG1 NTF3 NRXN1</b>
CACNA1C CCDC60 CCKAR	<b>NTNG2</b> <b>Myelin related</b> <b>MAG</b> <small>MPZL1</small> <b>QK1</b> <b>Cholinergic</b> <small>CHRNA7</small> <b>Oxidative</b>
CDKN2A CHN2 CHRM5	<b>stress ATP6 GCLM ND2 NDUFV2</b> <b>Immune/cytokine IL1A MICB</b>
CHRNA7 CLOCK COMT	<b>TRAF3IP1</b> <b>Signalling</b> <small>ADCYAP1</small> <b>ARHGEF10</b> <small>CDKN2A</small> <b>GNAL GNL3</b>
CSF2RA CSF2RB CSPG5	<b>ARHGAP18 MAPK14 GNB1L PLA2G4C PLAA PPP3CC</b>
CYTB DAO DAOA DBH	<b>PPP1R1B RAPGEF6 UHMK1 VRK2</b> <b>Structural MAP4</b>
DGCR2 DGCR6 DISC1 DKK4	<b>MYT1L</b> <b>MYH9</b> <b>TUBA8</b> <b>DiGeorge</b> <b>DGCR2 DGCR6</b> <b>Circadian</b> <b>CLOCK PER1</b>
DLX1 DRD2 DRD3 DRD4	<b>AHI1</b> <small>AK1</small> <b>ALDH3B1</b> <small>ANK3</small> <small>ARVCF</small> <b>ASTN2 BRD1 BTN2A2</b>
DRD5 DTNBP1 EGR2 ENO2	<b>BTN3A1</b> <small>CCDC60</small> <b>CCKAR CHN2 CSPG5</b> <small>DKK4</small> <b>ENO2</b>
ERBB2 ERBB3 ERBB4 FABP7	<b>FABP7</b> <small>FXVD6</small> <b>GRP78</b> <small>HIST1H2AH HIST1H2AG HIST1H2BJ</small> <b>KPNA3</b>
FBXL21 FEZ1 FGF14 FXR1	<b>KREMEN1</b> <small>PCDH8</small> <small>SLC1A3(GLUT)</small> <b>MDGA1 MC5R MCTP2</b> <small>DRD2</small> <small>CHRM5</small> <b>NPAS3 PNPO</b>
FXVD6 FZD3 GABBR1	<b>PTBP2</b> <b>RELN</b> <b>SHISA5 SIRT5 TAAR6 TSPAN8 TXND5</b> <small>YWHAZ</small>
GABRA1 GABRB2 GABRP	<b>YWHAZ</b> <small>ZDHHC8</small> <b>ZNF74</b> <small>CSF2RB</small> <small>DRD1</small> <small>SRR</small> <small>GRD1</small> <small>GABRA1</small> <small>SN</small> <small>SPARC1</small> <small>ZNF80A</small> <small>TSPO</small> <small>JARID2</small> <small>ITIH3</small>
GCLM GFRA1 GNAL GNB1L	<b>HOMER2</b> <small>ALDH1A2</small> <small>PDE4D</small> <small>MEGF10</small> <b>SLCO6A1</b> <small>NOTCH1</small> <b>DLX1</b> <small>ASCL6</small> <small>PRSS16</small> <small>UFD1L</small> <small>GRB4</small> <small>OPRM1</small> <small>HRH2</small> <small>KCNH2</small> <small>CYTB</small> <small>CSF3A</small> <small>NRG1</small> <small>PLSNA2</small> <small>NDEL1</small>
GNL3 GRIA3 GRIA4 GRID1	<small>FXR1</small> <small>IMP2</small> <small>GRM5</small> <b>SMARCC1</b> <small>NPTN</small> <small>NRG3</small> <small>GABBR2</small> <small>NTNG1</small> <small>PCDH8</small> <small>SLC17A3</small> <small>GRM7</small> <b>SLC17A7(PO4)</b> <small>DAO</small>
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 PCMI	
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	

TABLE 3: Continued.

SMARCC1 SNAP29 SP4 <sup>3</sup> SPARCL1 SRR SYN2 SYN <sup>H</sup> SYNGR1 SYT11 TAAR6 T <sup>H</sup> TPH1 TRAF3IP1 TSNAX TSPAN8 TUBA8 TXNDC5 UFD1L UHMK1 VRK2 YWHAE ZDHHC8 ZNF74 ZNF804A	
<b>Borrelia</b>	<b>Dopamine</b> ALDH1A2 <b>DRD2</b> DRD3 DRD4 DRD5 MAOB
<b>Burgdorferii</b>	<b>Serotonin</b> HTR1A HTR3C HTR6 HTR3D HTR3E SLC6A5 <b>TDO2</b>
<b>Number of SZ genes = 167</b>	<b>Glutamate</b> DAOA <sup>GLUL</sup> <b>GRIA3</b> GRIA4 GRIN1 GRIK1 GRIK3 GRIK5 <b>GRIN2A</b> GRM2 GRM3 GRM4 PRODH <b>SLC1A3</b> SLC1A5 SLC1A4
ABCA13 ACSL6 ADCYAP1 ADSS AGBL1 AH11 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 MYTIL NALCN ND2 NDE1 NDEL1 NDUFV2 NOS1 NPTN NRG1 NRG3 NRXN1 NTNG2 NUMBL PADI2 PCMI	<b>GABA</b> GABBR1 GABRB2 GAD1 GAD2 <b>Cholinergic</b> <b>CHRM5 synaptic</b> BLOC1S1 <b>CABIN1</b> CNTN4 <b>CPLX2</b> <b>DLG1</b> GPRASP2 <sup>GRIP1</sup> HOMER2 HOMER3 RGS4 <b>RGS9</b> <b>SHANK3</b> SNAP29 <b>SPTAN1</b> SYNGAP1 STXBP1 SYNGR1 SYN2 <b>SYN3</b> SYT5 <b>DISC1 related</b> DISC1 FEZ1 IMMT <b>MLC1</b> NDE1 <b>NDEL1</b> PCM1 PCNT PDE4B TSNAX <b>Neuregulin/ growth</b> EGR4 EGR2 ERBB4 FGF14 <b>NRG1</b> NRG3 <b>Immune</b> IL1RAPL1 <b>LIFR</b> TPI1 <b>Signalling</b> CSNK1D GSK3A <b>IMPA2</b> PIP4K2A PLA2G4C PLA2G4D SH3GL2 STK24 <b>Channels</b> CACNA1B CACNG2 KCNH5 KCNH6 <b>KCNN2</b> <b>Myelin</b> KCNQ5 CNP MOBP OMG <b>RTN4R</b> Structural ACTB ACTG1

TABLE 3: Continued.

PCNT PDE4B PDE7B PGBD1	<b>GFAP MAP1B</b> <sub>MAP2</sub> <b>MAP4 MYT1L</b> <sub>NEFL</sub> <b>TUBA1A</b> <sub>TUBA1B</sub>
PICK1 PIK3C2G PIP4K2A	
PLA2G4C PLAA PLXNA2	
PNPLA8 POM121L2 PPP1R1B	<b>Oxidative stress ATP5A1 ATP6V1A COX1</b> <sub>CRYM</sub>
PPP3CC PRKAG2 PRODH	
PRSS16 QK1 RAPGEF6 RELN	<b>GCLC</b> <sub>ND5</sub> <b>NDUFS3</b> <sub>NDUFV2</sub> <b>PRDX1</b> <sub>AKT1</sub>
RGS4 RGRIP1L RSRC1	
RTN4R SEMA3D SHANK3	
SLC17A1 SLC17A6 SLC17A7	<b>AADAT ABCA7</b> <sub>ADAM22</sub> <b>ADAMTS4 ADIPOQ AGLB1 AKR1D1</b>
SLC1A2 SLC1A3 SLC1A6	
SLC6A5 SLC6A1 SMARCA2	<b>AHI1 ALOX12 AP3D1 AP3M1</b> <sub>APOL2 APOL3 APOL4 APOL6</sub>
SMARCC1 SNAP29 SPARCL1	
SYN2 SYN3 SYNGR1 TAAR6	<b>ARHGDI1 ARID4B ASTN1 ATCAY ATP2B2 BAP1 BIVM</b>
TCF4 TDO2 TRAF3IP1	
TRMT2A TSNAX UFD1L	
USP46 VRK2 ZBED4 ZDHHC8	<b>BRD1</b> <sub>BTN3A1</sub> <b>CAD CAP1</b> <sub>CCDC60 CCDC141</sub> <b>CCKAR CDC42EP3 CEP63</b>
ZNF804A	
	<b>CHL1</b> <sub>CHN2</sub> <b>CLU CNTNAP2 CPS1 CTNND2 DBP DDAH1 DZIP1</b>
	<b>DNAJC6 DOCK9 DPYSL2</b> <sub>DRP2 EFN2 EIF4A2 ENO2 ENTPD4</sub>
	<b>EPHA6 ERLIN1 ERMN FABP3</b> <sub>FARSA FBXL21</sub> <b>FIGN FNIP1 FOLH1</b>
	<b>FOLH1B FOXP2 FSTL1</b> <sub>FTO</sub> <b>FZD3</b> <sub>GAPDH</sub> <b>GLRA2 GNPAT</b>
	<b>GMPS GPR18 GPR50 GPR125 HNRNPA2B1 HRH2</b> <sub>HS3ST2</sub>
	<b>HS6ST3 HSD11B1 HSPA8 HSPD1 ITIH4 KIAA0513</b>
	<b>KREMEN1 LRRTM1 MMS22L MYL12B NCOA7 NLGN4X NOVA1</b>
	<b>NR4A3 NRCAM NTNG2 NUBPL OLFM1 OPHN1 PADI2 PAK2 PAK3</b>
	<b>PCDHA3 PDE7B</b> <sub>PDE10A</sub> <b>PGAM1 PGBD1 PGK1 PGPPNPLA8</b>
	<b>PLXNA2 POMC POM121L2 PRKAG1 PRKAG2 PRKAG3</b>
	<b>PYGB RAI1</b> <sub>RAPGEF6</sub> <b>RELN RIMS2 RIT2 RORB RSRC1 SEL1L3</b>
	<b>SEMA3A</b> <sub>SEMA3D</sub> <b>SEPT4</b> <sub>GRIN2D</sub> <b>SIM1</b> <sub>SLC32A1</sub> <b>SLC17A1 SLC17A7</b>
	<b>SLC24A5</b> <sub>SLC25A14</sub> <b>SLITRK2 SMARCA2 SMARCC1</b>

TABLE 3: Continued.

	<p>SMARCE1 SPARCL1 SRD5A2 STRN TAAR6 TH1L</p> <p>TMTC4 TRIM3 UBAC2 UNC5C UGGT2</p> <p>UQCRC1 USP46 UTRN YWHAZ ZBED4 ZBTB20 ZDHHC8</p> <p>SLC39A2 KCN7 ALDH1A3 MTNR1A BRPF1 EPB41L1 ZNF804A CYP28B1 NR4A2 HSD11B2 SLC6A9 AK1 HSPD1 OFCC1 STGAL2 MCHR2 MEGF10</p> <p>ANKK1 PCDH11Y COX2 SEMA3B DGCR2 SLC06A1 PICK1 ANK3 HSPA12A SLC25A14 TRMT2A ATP10V1B2 VRK2 PCDH41 DRD1 ND2 ATP2A2</p> <p>GSPT1 NALCN MCTP2 HTR2A CHRNA7 CSF2RA GRIA1 FLA2G4C RCAN1 SLC26A6 KONE2 ACSL6 NOS1 BAB FAM8A1 ST7 DDO</p> <p>ASTN2 ERVWE1 GRM5 GNAL SEPT7 NBEAL2 GABRG1 GRM2 KIF21A NCS1 ACS5 JARID2 PSMD10 KCNKB NUMBL RIC3</p> <p>BRPF3 MBLN2 SPA17 KCNN3 SLC1A6 LSAMP RPGRIP1L SETD2 ABCA13 PIK3C2G GRM7 AP3B2 IPO5 JAG1 NRXN3 ATF7IP UFD1L</p> <p>MAGE2 PCDH12 HIF13A NEFH DGKI CYIP1 ALDH3B1 RLBP1 MCF2 SLC17A6 MAP6 NDUFS1 TCF4 SNX6 PPP3CC SGCE MES</p> <p>ORC3 C10orf3 TRAF3IP1 MM BPRF3 ATP6V0D1 DCDC2 PPT1 KCNB9 WDR1 HSPA8 CRYAB SLC1A2 APP</p> <p>TMEM200A CLINT1 HDAC9 PAICS MTF3 NPTN PPP1R1B GRB5 NR3C1 QK1 PLAA PURA EP3D SMG6 ASTN2</p> <p>PRKAR2A MPDZ SC5DL</p>
	<p><b>Human gene products</b></p>
HERV-W no filter	<p>Glutamate related <b>GLUL</b> Synaptic <b>SPTNB5 GNB2 SHANK3</b></p> <p><b>PDZRN4</b> DISC1 related <b>DISC1</b> Neuregulin and growth <b>FLT4 NEURL4</b></p>
Number of SZ genes = 13	<p><b>NLGN4X NRG3</b> Myelin related <b>MYL6B</b> Oxidative stress</p> <p><b>ATP11A COX11</b> Channels Calcium <b>CATSPERG</b></p>
CACNG2 CYP1A2 DISC1 DTNBPI HLA-DRB1 MAD1L1 MED12 MYO18B NOS1 NRG3 SHANK3 SP4 XRCCI	<p><b>CACNG2 ITPR3</b> Potassium <b>KCNN1 KCNJ16</b> Oxidative stress <b>PYROXD2</b> Immune /cytokine <b>CHIITA DEFA7P</b></p> <p><b>TNFAIP3 CSF3R</b> Structural <b>COL6A3 DNM2 MYO18B</b></p> <p><b>MYBPC1</b> Signalling <b>PDE4C</b> <b>PLA2R1 PLCB3 PLHDA2</b></p> <p><b>PLA2G4A PRICKLE1(wnt)</b> <b>ABCA2 ABCA5 ABLIM3</b></p> <p><b>ADAM29</b> <b>ADAMYTSL2 AIM1L AKR1B15 ALG9 ANKRD11 ANXA1</b></p> <p><b>ARID2</b> <b>ARSE BET1L CCDC51 CENPE CEP152</b></p> <p><b>CDH11</b> <b>CHD23 CYFIP1 CYP1A2 DHTKD1</b> <b>DPYSL5 DST EDC4</b></p>

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 PSAC1 VPS13B SSX10 INTS8 OGN KLHDC8A HPS1

PAQR6 RUFY1 ASPM TTN GNA12 CFSF2 FBXW5 DTNBP1 DISC1 ARGLU1 FAM48B LSM14B CKAP5 UTRN ERVFRDE1 SHITC1 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	<p><b>PDZRN3 syntaxin 16</b> Neuregulin and growth</p> <p><b>ERBB3</b> NRG1 NRG2 UTRN <b>DISC1 related</b> <small>DISC1</small> <b>PCNT</b></p> <p>Translation initiation <small>EIF3A</small> <b>EIF3K</b> <small>EIF4G2</small> Oxidative stress</p> <p><b>ACOX2</b> cytochrome c oxidase subunit II NADH dehydrogenase</p> <p>subunit 1 NADH dehydrogenase subunit 2 <b>Glycine receptors</b> <small>GLRA1</small> <small>GLRA2</small> <b>GLRA3</b> <small>GLRA4</small> <b>Calcium</b> voltage-dependent L-type calcium channel subunit <b>Immune/cytokine</b> NFATC4 <b>TNFRSF1B</b> <b>TLR4</b> <b>TNFSF10</b> immunoglobulin heavy chain IFT122 <b>Signalling</b> <small>NFKBIL2</small> <small>PIK3CA</small> <b>SOS1</b> <b>Structural</b> <b>ACTRT2</b> <b>COL6A5</b> <small>ABC6</small> <small>ACE</small> <small>ACTRT1</small></p> <p>ADNP <small>AKAP6</small> ANXA1 <small>ANXA4</small> <b>APOBEC1</b> <small>APIG2</small> AQP7 ARMC7</p> <p>ASB1 BAT2L1 <small>CCDC135</small> <b>CCS</b> <b>CCT6B</b> <small>CDC14A</small> <b>CDKL3</b> CENPA</p> <p>CEP192 <small>CNGA4</small> <b>CNOT1</b> CNTNAP5 CP CREG2</p> <p>CRIM1 CRIPAK <small>CSE1L</small> <b>DCLRE1A</b> <small>DDX5</small> DENND3 <small>DOCK1</small></p> <p>EDNRA <small>EFHC1</small> <b>ECHDC2</b> ESYT1 <small>EXOC6</small> <small>FAM123A</small> <small>FCHSD1</small> <b>FUBP1</b> <small>GCNT6</small></p> <p>GLT8D2 <small>GLTSCR1</small> GNAO1 GPR153 GSDMD HTT <b>IPO5</b> ISM2</p> <p>KIFC2 KREMEN1 KRT76 LIPN <small>LRRTM1</small> LRRC61</p> <p>LRRC14B <small>LRRIQ1</small> <b>MAN1B1</b> <small>MAP7D1</small> MBOAT7 MRAP <b>MTMR2</b> <small>MGAT5B</small> <small>NOP58</small> <b>NR2F6</b> <b>NWD1</b> <small>PLEC</small> <small>PHC3</small> <b>PHLPP2</b> <b>POM121L12</b></p> <p>PPFIA4 PRL <small>PRX</small> <small>RAB15</small> <b>RBPJ</b> <small>RPM12B</small> <b>RSPH9</b> <small>RHOBTB2</small> SCAPER <b>SEC22A</b></p>
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TABLE 3: Continued.

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	<p>SENP7 SIPA1L2 SLC22A15 SLC26A9 SLC40A1 SMTLN1 SNAI1 SNTG1 STAC3</p> <p>TABC1<sub>TAS2R20</sub> TCHH TMEM63A TMEM143<sub>TMEM163</sub> TMIGD2 TM4SF4 <small>... RSPH9</small></p> <p><small>ANKK2 TTN RABRA</small> TAS2R31 TRIM33 TROAP TYK2<sub>SPC25</sub> THADA UPF2</p> <p>UBR3 UMODL1<sub>LOXHD1</sub> APIG2<sub>PNPLA8</sub> XPO5 ZFP2 ZNF219 ZFPM1 ZNF391<sub>LIPF</sub> <small>...</small></p> <p><small>COGAA6 NF1 ... PSEN2 PAEN DELEC1 PIAS2 GTPBP1 calcium channel, voltage-dependent, L type, alpha 1C subunit PROX1 SNRK ... GAS6 IL4 TMTC4 GNA11 HOMER SPTY2D1 DNAH8 ADH1 ...</small></p> <p><small>... PDZL2 ... calcium channel alpha 1G TTC25 ... TAZB4 GRBIP ...</small></p>
Rubella: no filter	<p>Cholinergic <b>CHRNA3 ACHE</b> Dopamine receptors <small>dopamine receptor isoform short</small></p> <p><b>DRD4</b> Serotonin receptors <b>HTR3C</b><sub>HTR3D</sub> Glutamate receptors <small>GRM2</small></p>
Number of SZ genes = 21	<p><b>gluR7 GRIK2</b> <small>GRIK3 GRIK4 GRIK5</small> NMDA receptor subunit epsilon</p> <p>2 NMDA receptor subunit epsilon-3 NMDA receptor subunit epsilon-4 <small>PRODH GILRT</small> GABA <b>GABA transporter 1</b> Synaptic</p> <p><b>GRASP HIPK4 SYNPO PDZD7</b><sub>SHANK3 SYNCRIP</sub> DISC 1 related <small>DISC1</small></p>
DRD4 EGR4 ENAH ERBB2 FLNB GNAS GRIK2 GRIK3 GRIK4 GRIN2B GRIN2D HLA-A HLA-B HLA-DRB1 NOS1 NRG2 NRXN1 PRODH SHANK3	<p>Neuregulin and growth <small>erbB-2</small> <b>NRG2 GDF1</b> IGFBP3 Translation initiation</p> <p><b>EIF3A E2F1</b> Channels Calcium <b>CACNAB1 CACNA1E</b> Signalling</p> <p><small>GRB10</small> <b>RASSF7</b> <small>INPPL1 PTPRK PPP1R14C</small><sub>MAP3K13</sub> Immune cytokine</p> <p><b>HLA-A</b> <small>HLA-B</small> <b>MDR/TAP IL17D</b> Structural <b>ACTN4 COL1A1</b></p> <p><b>COL7A1MYH14</b></p> <p>ABTB2 ADAMTSL5 <small>ADRA1D</small> <b>AKAP5</b> AKNA AIPL1 ARHGAP30 BAALC BST1</p> <p><b>CECR6</b> <small>CHAC2</small> <b>CKAP4</b><sub>CTDP1 DCAF8L2</sub> ENAH<sub>EPN3</sub> <b>FARS2</b></p> <p><b>FLNB</b><sub>HCG4P6</sub> <b>HMGN1</b> INA IQSEC2 ITGA8 ITGB4<sub>KLHL4</sub></p> <p><b>KLHDC4 LARP1</b> LEMD2 <b>MED23 MFSD6</b> MON1B</p> <p><b>MRVIL</b><sub>MYO1B NCRNA00265</sub> <b>NSAP1</b><sub>NTN1 NXF5</sub> OPMCL <b>OS9</b><sub>OTOP1</sub></p>

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TABLE 3: Continued.

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**PARP9 PGAM5 PIGZ POM121 PTGER3 PYCRL**  
**RNF128 SALL3 SASH1 SEC16A SEMA6C SEMAZ** SRP68  
**SLC4A3 SLC20A2 SOX4 SPAST SPHKAP SRD5A1** SRCAP  
**STARD9 STRA13 TFAP2B** THEG **TFAP2C**  
**TFAP2E** THSD7A **TJP3 TMC1 TMEM31** TMC8 **TNKS2 TNRC18**  
**UNC5A VDRIP WAPAL WIPF3 WDR86**  
**Z3CH3 Z3CH4 ZC3HAV1 ZFP36L2 ZP1 ZYX** ADO

---	---	PIC11	---	---	CHD5	WDR20
---	PARVA	---	HMGAI	---	---	---
REM2	---	ELAVL1	---	MAN2A2	---	SSPO
---	hnRNP Q2	GFR35	---	NEBP2	---	TRAP2A
---	CCDC39	---	PCSK7	---	RASAL3	KIF3
GNAS	---	---	MELT19	PHC2	---	SERP9
TNPO2	HOOK2	---	---	CDK2L	AGXT2	MEGF6
receptor interactor	---	ZNF584	---	integrin, alpha 5	---	Fc- $\beta$ receptor beta

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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 burgdorferi* 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 <sup>""</sup>		
KDM1A amine oxidase demethylase		
KDM1B <sup>""</sup>		
MAOA monoamine oxidase	SLC6A2 (Noradrenaline)	CADPS2 amine release activator
MAOB <sup>""</sup>	SLC6A3 (Dopamine)	CDCA7 cell division cycle associated 7
RNLS renalase amine oxidase	SLC18A1 vesicular monoamine	CDCA7L
SMOX spermine oxidase	SLC18A2 <sup>""</sup>	IL4I1 cytokine
SPR sepiapterin reductase	SLC22A2 organic cation	PICK1 postsynaptic scaffold
Monoamine synthesis cofactor	SLC22A3 extraneuronal monoamine	
SULT1A1 sulphotransferases	SLC29A4 (Na <sup>+</sup> /H <sup>+</sup> )	
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 armory 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 immunoabsorption techniques might therefore also be of 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.

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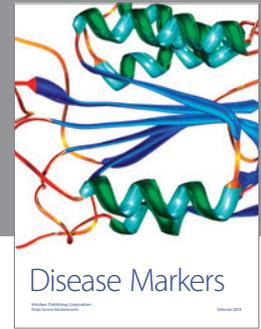
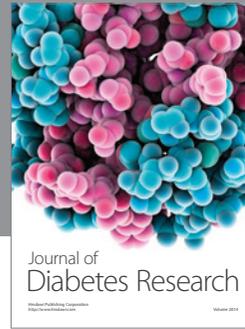
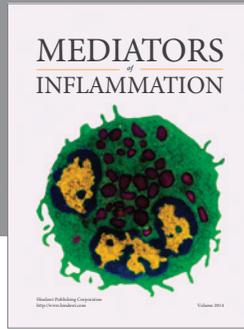
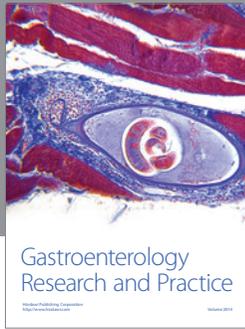
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