REVIEW ARTICLE

GENOME-WIDE ASSOCIATION STUDIES IN SCHIZOPHRENIA, AND POTENTIAL ETIOLOGICAL AND FUNCTIONAL IMPLICATIONS OF THEIR RESULTS

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Summary: Background: Despite the fact that the genetic basis of schizophrenia has been intensively studied for more than two decades, our contemporary knowledge in this field is rather fractional, and a substantial part of it is still missing. The aim of this review article is to sum up the data coming from genome-wide association genetic studies in schizophrenia, and indicate prospective directions of further scientific endeavour. Methods: We searched the National Human Genome Research Institute's Catalog of genome-wide association studies for schizophrenia to identify all papers related to this topic. In consequence, we looked up the possible relevancy of these findings for etiology and pathogenesis of schizophrenia using the computer gene and PubMed databases. Results: Eighteen genome-wide association studies in schizophrenia have been published till now, referring to fifty-seven genes supposedly involved into schizophrenia's etiopathogenesis. Most of these genes are related to neurodevelopment, neuroendocrinology, and immunology. Conclusions: It is reasonable to predict that complex studies of sufficiently large samples, involving detection of copy number variants and assessment of endophenotypes, will produce definitive discoveries of genetic risk factors for schizophrenia in the future.

Key words: *Schizophrenia; Genome-wide association studies; Neurodevelopment; Neuroplasticity; Neuroendocrinology; Immunology*

Introduction

Schizophrenia (SZ) is a chronic disabling disease of the brain. SZ affects 0.5–1 percent of the adult population worldwide. It is commonly manifested by auditory hallucinations, paranoid or bizarre delusions, and disorganized speech and thinking. Schizophrenia results in a significant social or occupational dysfunction. Nine to thirteen percent of patients with schizophrenia eventually commit suicide (9). The causes of SZ consist of genetic and environmental factors (27). Heritability of schizophrenia is usually mentioned in the range 0.4–0.7 (32). Even though we already have certain empirical data about the genetic basis of schizophrenia that implicate specific DNA loci (17), our recent knowledge on the genetics of schizophrenia is still nascent.

A genome-wide association study (GWAS), also known as a whole genome association study (WGAS), is an examination of frequencies of single nucleotide polymorphisms in most of the genes of different individuals with vs without a certain disease in order to see how much the polymorphisms in genes vary among the affected (cases) as against the unaffected subjects (controls). The individuals are tested for single DNA mutations (single-nucleotide polymorphisms, SNPs), but GWASs are also able to detect copy number variants (CNVs; DNA deletions or duplications). A common practice is that the original GWAS is subsequently replicated by the same authors in an independent sample. GWASs incorporate the power to detect small effects with the advantage of the positional genetics design, which requires no specific knowledge of pathogenesis. The first genome-wide association study of age-related macular degeneration appeared in 2005 (19). Since then, more than one thousand GWAS articles have been published in the National Human Genome Research Institute (NHGRI) GWAS Catalog (30), as accessed on the 23rd of September, 2011. The NHGRI is one of the 27 National Institutes of Health established pursuant to federal legislation in the U.S. GWASs are usually useful in finding the molecular pathways of the disease (47). Genome-wide association studies recently represent the most comprehensive procedure to discover a genetic background of complex diseases.

The aim of this article is to sum up the recent GWAS findings in SZ patients, and imply their possible significance in schizophrenia etiopathogenesis.

Methods

We searched the NHGRI GWAS Catalog (30) for Schizophrenia on 25th September 2011. Afterwards, we attempted to ascertain the potential etiopathogenetic role of

the genes found to be associated with SZ using computer gene databases (28, 46). Lastly, we discussed a prospective meaning of these findings, their limitations, and the direction for a further research.

Results

Eighteen relevant published GWAS studies were found by a selecting program. Their key description and results are displayed in Tables 1a and 1b.

The potential etiologic and functional role of the genes associated with schizophrenia according to the presented GWASs is shown in Tables 2a, 2b, and 2c (28, 46).

Note: In the Tables 2a, 2b, and 2c, the genes related to neurodevelopment and neuroplasticity are written in bold. Names of the genes in relation to immunology are in italics and the genes related to neuroendocrinology are underlined. The association studies for each gene can be found at http://www.schizophreniaforum.org (Schizophrenia Research Forum).

For most genes listed in Tables 2a, 2b, and 2c, no results were found in the PubMed database (29) on the 4th of October, 2011 using the name of the gene and schizophrenia as key words. Nevertheless, a possible role of certain genes in schizophrenia etiology and pathophysiology was already mentioned. This is recapitulated in the following text.

According to Berretta (6), emerging evidence points to the involvement of the brain extracellular matrix (ECM) in the pathophysiology of schizophrenia. Solid evidence supports the involvement of reelin, an ECM glycoprotein related to corticogenesis, synaptic functions and glutamate NMDA receptor regulation. Reelin is expressed prevalently in GABAergic neurons, which secrete it into the ECM. Marked changes of reelin expression in SZ have typically been reported in association with GABA-related abnormalities. ECM anomalies may contribute to disrupted connectivity and neuronal migration, synaptic abnormalities and altered GABAergic, glutamatergic and dopaminergic neurotransmission in schizophrenia.

PRODH (proline dehydrogenase) gene, encoding proline oxidase (POX), has been associated with schizophrenia through linkage, association, and the 22q11 deletion syndrome (16). The PRODH gene polymorphisms are related to structure, function, and connectivity of striatum and prefrontal cortex, which was found in a family-based sample. This circuitry is implicated in the pathophysiology of schizophrenia. The schizophrenia risk haplotype was associated with decreased striatal volume and increased striatal-frontal functional connectivity. According to Li et al. (24), PRODH gene was associated with executive function in schizophrenic families (N = 167) in China.

Wang et al. (45) summed up the knowledge on the role of the NOTCH4 locus (neurogenic locus notch homolog protein 4) in SZ. The NOTCH4 gene was found to be associated with schizophrenia among the British population in 2000. The results from independent studies are inconsistent. Allelic heterogeneity, heterogeneity of clinical diagnosis, ethnic variance of researched population, and linkage disequilibrium structures may be the reasons for a poor replication. A part of the studies suggested that the NOTCH4 gene could play a role in a subgroup of the disease, such as early-onset schizophrenia and negative symptoms. A single study revealed a strong association with the frontal lobe cognitive performance. According to Wang et al. (45), the NOTCH4 gene may be associated with schizophrenia, but we do not still know how the gene contributes to the etiology of this illness.

Roussos et al. (38) revealed that the ANK3 (ankyrin 3) rs9804190 C allele was associated with lower ANK3 mRNA expression levels, higher risk for schizophrenia, and poorer working memory and executive function performance in the case-control analysis in SZ patients (N = 272) versus healthy controls (N = 513).

Lennertz et al. (23) analysed the impact of the TCF4 (transcription factor 4) variant rs9960767 on early information processing and cognitive functions in schizophrenic patients (N = 401). TCF4 influenced verbal memory in the Rey Auditory Verbal Learning Test. TCF4 did not impact on various other cognitive functions in the domains of attention and executive functions. The SZ risk allele C of TCF4 rs9960767 reduced sensorimotor gating as measured by prepulse inhibition in electrophysiological examination. This indicates that TCF4 influences key mechanisms of information processing, which may contribute to the pathogenesis of schizophrenia. The role of the SZ risk allele C of the TCF4 rs9960767 polymorphism in disrupting sensorimotor gating in schizophrenia spectrum and healthy volunteers was also confirmed by Quednow et al. (36).

Based on a systematic review of literature, Crespi et al. (11) concluded that the HLA-DRB1*13 alleles are associated with a higher risk of schizophrenia compared to the HLA-DRB1*04 alleles. The risk of individual DRB1 (DR beta 1) variants for rheumatoid arthritis is quite the opposite. These findings from genetics and epidemiology imply that a subset of schizophrenia cases may be underlain by genetically based neuroimmune alterations. Analyses of the causes of risk and protective effects from DRB1 variants may provide new approaches to therapy.

According to Krug et al. (20), neurogranin is the main postsynaptic protein regulating the availability of calmodulin-Ca^{++} in neurons. Neurogranin is expressed exclusively in the brain, particularly in dendritic spines and has been implicated in spatial learning and hippocampal plasticity. Krug et al. having used cognitive tests and functional magnetic resonance imaging in a large sample of healthy subjects demonstrated that rs12807809 of the neurogranin gene is associated with differential neural functioning in the anterior and posterior cingulate. These areas are involved in episodic memory processes and have been implicated in the pathophysiology of SZ in structural and functional imaging as well as post mortem studies.

Hashimoto et al. (13) mentioned that functional magnetic resonance imaging studies in healthy subjects demonstrated the association of the ZNF804A (zinc finger protein 804A) variants with neural activation during a memory task. In their

own research of 113 patients with schizophrenia and 184 healthy subjects, Hashimoto et al. investigated the potential relationship between the ZNF804A rs1344706 polymorphism and memory function. Patients with SZ exhibited poorer performance on verbal memory, visual memory, attention/concentration and delayed recall as compared to healthy control subjects ($P < 0.001$). Patients with the high-risk ZNF804A T/T genotype scored significantly lower on visual memory than the G carriers did ($P = 0.018$). This data suggests that the ZNF804A gene rs1344706 polymorphism may be related to memory dysfunction in schizophrenia.

According to Bennett (5), gray matter loss in the cortex is extensive in schizophrenia, especially in the prefrontal-temporal-network (PTN). Several molecules such as neuregulin-1 (NRG1) and its ErbB4 receptor are encoded by candidate susceptibility genes for schizophrenia. It is suggested that one pathway involves NRG1/ErbB4 determining the efficacy of N-methyl-D-aspartate receptors (NMDARs) found on dendritic spines at synapses in the PTN. Another pathway involves NRG1/ErbB determining the proliferation and differentiation of oligodendrocytes in the white matter as well as their capacity for myelination. In schizophrenia, a causal chain is established between dysfunctional products of susceptibility genes, the decrease of dendritic spines and synaptic terminals, and the loss of gray matter. Similarly, Pitcher et al. (34) propose that NRG1-ErbB4 signalling participates in cognitive dysfunction in SZ by the aberrant suppression of Src-mediated enhancement of synaptic NMDARs function.

The possible involvement of the PTGS2 (prostaglandin-endoperoxide synthase 2) gene and inflammatory mechanisms in etiopathogenesis of schizophrenia may be the explanation for the antipsychotic effect of the anti-inflammatory COX-2 inhibitors (26).

Discussion

According to Duan et al. (12), the data proceeding from GWAS studies provide evidence for: 1. A number of chromosomal regions with common polymorphisms showing genome-wide association with schizophrenia, but only presenting small odds ratios. 2. Polygenic inheritance. 3. Involvement of rare (< 1%) and large (> 100 kb) copy number variants (CNVs) that have fairly large effect sizes on disease risk. 4. A genetic overlap of schizophrenia with autism and bipolar disorder.

Several candidate genes involved in neurodevelopment have been suggested in schizophrenia by the GWAS studies (EFHD1, EML5, RELN, ANK3, TCF4, NRG1, LNX2 etc.). Therefore, the genetic basis of schizophrenia could involve different factors more or less specifically required for neuroplasticity, including the synapse maturation, as well as neurogenesis.

The presence of cytokine receptor abnormalities in schizophrenia may help to explain prior epidemiologic data relating the risk for this illness to altered rates of autoimmune disorders, prenatal infection and familial leucemia (22).

We can sum up, that the results of GWAS studies implicate the significance of neurodevelopmental, neuroplastic, neuroprotective, neuroendocrinological, and immunological factors in etiology and pathogenesis of schizophrenia.

Although the new data from GWASs in schizophrenia are promising, they still do not meet our initial expectations (8). An obvious question is why the results of genome-wide association studies in schizophrenia do not correspond with the findings of earlier association studies aimed only at several genes or polymorhpisms? These previously discovered genes were reviewed by Schwab et al. (39). The authors covered the Regulator of G-protein signalling 4 (RGS4), d-Amino acid oxidase activator (G72; DAOA), Neuregulin 1 (NRG1), Dystrobrevin binding protein 1 (dysbindin), Phosphatidylinositol-5-phosphate-4-kinase type II-alpha (PIP4K2A), V-Akt murine thymoma viral oncogene homologue 1 (protein kinase B) (AKT1), several dopamine receptors (DRD1, DRD2, DRD3, DRD4), and Disrupted in schizophrenia (DISC1) genes. This might indicate that effect sizes previously reported in schizophrenia non-GWAS genetics might have been overestimated.

Another problem in schizophrenia genetics is that rare variants with large effect have a very low frequency in the general population and therefore will not be detected by the population-based GWAS strategy. This may be overcome by studying families and ethnically homogenous populations (2).

The reason why the results of individual GWASs in schizophrenia do not overlap may lie in the fact that they do not cover the same polymorphisms. The dissimilar results may also be explained by clinical or ethnic differences among the studied populations.

Among clinical factors, variability of the phenotype is a major limitation in genetic research of schizophrenia (7). Genetic problems include locus heterogeneity and the complex genetic architecture of the phenotype. Some genes may be disease-causing, whilst others only disease-modifying in each individual. Endophenotypes instead of the complex nosological entity of schizophrenia may be more appropriate for a genetic research because of their good detectability, and a relative simplicity (3).

The Psychiatric GWAS Consortium systematically conducts GWAS meta-analyses. Past experiences suggest that for some disorders as many as 20,000 to 30,000 case subjects and similar number of comparison subjects are required to obtain highly robust findings (35). This may be the arrangement in future SZ genetic studies.

According to Lee et al. (21), there is a pressing need to better integrate the multiple research platforms including biology computational models, genomics, epigenetics, cross disorder phenotyping studies, transcriptomics, proteomics, metabolomics, neuroimaging and clinical correlations in the studies on psychoses, including schizophrenia.

Conclusions

The up to now results of GWAS studies point out that the genetic background of schizophrenia is mostly related to neurodevelopmental, neuroendocrinological, and immuno-

logical factors. It is reasonable to predict that elaborate studies of sufficiently large samples will produce definitive discoveries of genetic risk factors for schizophrenia in the future.

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Tab. 1a: The survey of genome-wide association studies in schizophrenia

Study	Initial Sample Size	Replication Sample Size	Genes Associated with Schizophrenia	P-value for the Best Supported Locus	Best OR [95% CI]
Alkelai et al., 2011 (1)	189 Arab Israeli individuals from 57 nuclear families	627 European ancestry cases, 541 European ancestry controls	LRRFIP1 UGT1 EFHD1	1.22×10^{-11}	3.75 [Not stated]
Chen et al., 2011 (10)	1,658 European ancestry cases, 1,655 European ancestry controls	5,203 European ancestry cases, 5,277 European ancestry controls, 1,875 Irish individuals, 1,142 African American cases, 985 African American controls	PTPN21 EML5	1.1×10^{-3}	0.92 [0.86–0.97]
Rietschel et al., 2011 (37)	1,169 European ancestry cases, 3,714 European ancestry controls	7,303 European ancestry cases, 26,274 European ancestry controls	AMBRA1 DGKZ CHRM4 MDK	3.89×10^{-9}	1.25 [Not stated]
Alkelai et al., 2011 (2)	331 Jewish-Israeli family members	189 Arab-Israeli individuals, 57 Arab-Israeli nuclear families	DOCK4 CEACAM21 PGBD1 RELN PRODH	9.61×10^{-8}	3.278 [Not stated]
Ma et al., 2011 (25)	98 Chinese cases, 60 Chinese controls	Not reported	MSRA	1×10^{-5}	Not stated
Yamada et al., 2011 (48)	120 Japanese parent-child trios	506 Japanese cases, 506 Japanese controls, 284 Chinese quads, 9 Chinese trios	ELAVL2	8.7×10^{-4}	Not stated
Ikeda et al., 2011 (14)	560 Japanese cases, 548 Japanese controls	1,511 Japanese cases, 2,451 Japanese controls, 479 U.K. cases, 2,938 U.K. controls	SULT6B1 NOTCH4	3.7×10^{-5}	Not stated
Athanasiu et al., 2010 (4)	201 Caucasian cases, 305 European controls	2,663 European cases, 13,780 European controls	PLAA ACSM1 ANK3	2×10^{-6}	1.16 [Not stated]
International Schizophrenia Consortium et al., 2009 (15)	3,322 European descent cases, 3,587 European descent controls	4,692 European descent cases, 15,493 European descent controls	HIST1H2AH RPL10P2 TCF4 FLYWCH1P1 RPL32P10 RPL7P9 PTBP2	1×10^{-8}	1.44 [Not stated]

Tab. 1b: The survey of genome-wide association studies in schizophrenia

Study	Initial Sample Size	Replication Sample Size	Genes Associated with Schizophrenia	P-value for the Best Supported Locus	Best OR [95% CI]
Shi et al., 2009 (40)	2,681 European ancestry cases, 2,653 European ancestry controls, 1,286 African American cases, 973 African American controls	5,327 European ancestry cases, 16,424 European ancestry controls	HIST1H2AH RPL10P2 HLA–DRB1 HLA-DQA1	1×10^{-8}	1.28 [Not stated]
Stefansson et al., 2009 (42)	2,663 European cases, 13,498 European controls	10,282 European cases, 21,093 European controls	PRSS16 TRNAI28P NOTCH4 SPA17 NRGN TCF4 EIF2S2P7 VRK2 SLCO6A1 PAM TLR4 DBC1	1×10^{-12}	1.23 [Not stated]
Need et al., 2009 (31)	871 European ancestry cases, 863 European ancestry controls	1,460 European ancestry cases, 12,995 European ancestry controls	No genome-wide significant association	N.S.	Not stated
Kirov et al., 2009 (18)	574 cases, 605 controls, 1,148 parents of cases	Not reported	CCDC60	1×10^{-6}	Not stated
O'Donovan et al., 2008 (33)	479 cases, 2,937 controls	6,666 cases, 9,897 controls	ZNF804A OR2BH1P RPL7AP58 SHISA9	2×10^{-7}	1.16 [Not stated]
Walsh et al., 2008 (44)	150 cases, 268 controls	83 children, 154 parents	NRG1	< 0.05	Not stated
Sullivan et al., 2008 (43)	738 cases, 733 controls	Not reported	AGBL1 PDC PTGS2 C1orf187 AGTRAP MTIF3 LNX2 ACSM1 FTHL8 AFF2	2×10^{-6}	6.01 [Not stated]
Shifman et al., 2008 (41)	660 cases, 2,271 controls	2,274 cases, 4,401 controls	RELN	9×10^{-7}	1.58 [1.31–1.89]
Lencz et al., 2007 (22)	178 cases, 144 controls	Not reported	CSF2RA IL3RA	3.7×10^{-7}	Not stated

Tab. 2a: The potential etiologic and functional role of genes associated with schizophrenia according to the genome-wide association studies

Gene	Location	Official Full Name	Function
LRRFIP1	2q37.3	Leucine rich repeat (in FLII) interacting protein 1	A component of the platelet cytoskeleton
UGT1	2q37	UDP glucuronosyltransferase 1 family	An enzyme that transforms steroids, bilirubin, hormones, and drugs
EFHD1	2q37.1	EF-hand domain family, member D1	A protein increasingly expressed during neuronal differentiation
PTPN21	14q31.3	Protein tyrosine phosphatase, non-receptor type 21	A signalling molecule that regulates cell growth and differentiation
EML5	14q31.3	Echinoderm microtubule associated protein like 5	A protein which plays a role in the regulation of cytoskeletal rearrangements during neuronal development and in adult brain
AMBRA1	11p11.2	Autophagy/beclin-1 regulator 1	A protein inducing autophagy, involved in neurodegeneration
DGKZ	11p11.2	Diacylglycerol kinase, zeta	A protein which may attenuate protein kinase C activity
CHRM4	11p12-p11.2	Cholinergic receptor, muscarinic 4	A G protein-coupled receptor inducing cellular responses
MDK	11p11.2	Midkine (neurite growth-promoting factor 2)	A retinoic growth factor which promotes angiogenesis, cell growth, and cell migration
DOCK4	7q31.1	Dedicator of cytokinesis 4	A protein involved in regulation of adherens junctions between cells
CEACAM21	19q13.2	Carcinoembryonic antigen-related cell adhesion molecule 21	A protein involved in cell adhesion
PGBD1	6p22.1	PiggyBac transposable element derived 1	An enzyme catalysing the movement of the transposon
RELN	7q22	Reelin	A protein thought to control cell-cell interactions critical for neuronal migration during brain development
PRODH	22q11.21	Proline dehydrogenase (oxidase) 1	A mitochondrial protein that catalyses the proline degradation
MSRA	8p23.1	Methionine sulfoxide reductase A	An enzyme repairing oxidative damage to proteins, may be related to cognitive functions
ELAVL2	9p21	ELAV (embryonic lethal, abnormal vision, Drosophila)-like 2	A neural-specific RNA-binding protein
SULT6B1	2p22.2	Sulfotransferase family, cytosolic, 6B, member 1	An enzyme involved in the metabolism of drugs and hormones
NOTCH4	6p21.3	Notch 4	A protein regulating interactions between physically adjacent cells, plays a role in a vascular development
PLAA	9p21	Phospholipase A2-activating protein	A signalling molecule that regulates the production of prostaglandins and tumour necrosis factor TNF-alpha
ACSM1	16p12.3	Acyl-CoA synthetase medium-chain family member 1	A protein involved in fatty acid metabolism
ANK3	10q21	Ankyrin 3	A protein playing key roles in motility, activation, proliferation, and contact of neurons
HIST1H2AH	6p21.33	Histone cluster 1, H2ah	A protein functioning in the compaction of chromatin into higher order structures
RPL10P2	6p22.1	Ribosomal protein L10 pseudogene 2	A pseudogene conserved in ribosomes

Tab. 2b: The potential etiologic and functional role of genes associated with schizophrenia according to the genome-wide association studies

Gene	Location	Official Full Name	Function
TCF4	18q21.1	Transcription factor 4	A protein important in nervous system development, memory and cognition
FLYWCH1P1	3q26.33	FLYWCH-type zinc finger 1 pseudogene 1	A pseudogene playing a role in cell growth and differentiation of embryonic stem cells
RPL32P10	3q26.33	Ribosomal protein L32 pseudogene 10	A pseudogene conserved in ribosomes
RPL7P9	1p21	Ribosomal protein L7 pseudogene 9	A pseudogene conserved in ribosomes
PTBP2	1p21.3	Polypyrimidine tract binding protein 2	A protein implicated in controlling of other splicing-regulatory proteins
HLA–DRB1	6p21.3	Major histocompatibility complex, class II, DR beta 1	A protein playing a central role in the immune system by presenting peptides from extracellular proteins
HLA-DQA1	6p21.3	Major histocompatibility complex, class II, DQ alpha 1	A protein playing a central role in the immune system by presenting peptides from extracellular proteins
PRSS16	6p21	Protease, serine, 16 (thymus)	A serine protease expressed exclusively in the thymus, playing a role during the selection of T cells
TRNAI28P	6p22.1	Transfer RNA isoleucine 28 (anticodon AAU) pseudogene	A pseudogene inable to encode RNA
SPA17	11q24.2	Sperm autoantigenic protein 17	A protein present at the cell surface functioning in cell-cell adhesion, and immune cell migration
NRGN	11q24	Neurogranin (protein kinase C substrate, RC3)	A protein which is a direct target for thyroid hormone in human brain, underlaying consequences of hypothyroidism on mental states during development and in adults
EIF2S2P7	2p16.1	Eukaryotic translation initiation factor 2, subunit 2 beta pseudogene 7	A nonfunctional DNA sequence unable to initiate translation
VRK2	2p16.1	Vaccinia related kinase 2	A serine/threonine protein kinase expressed in actively dividing cells
SLCO6A1	5q21.1	Solute carrier organic anion transporter family, member 6A1	An anion transporter
PAM	5q14-q21	Peptidylglycine alpha-amidating monooxygenase	A multifunctional protein which catalyzes neuroendocrine peptides
TLR4	9q33.1	Toll-like receptor 4	A protein involved in the production of cytokines
DBC1	9q32-q33	Deleted in bladder cancer 1	A protein important in bladder cancers
ZNF804A	2q32.1	Zinc finger protein 804A	A protein associated with a reaction time to a conflicting information
OR2BH1P	11p14.1	Olfactory receptor, family 2, subfamily BH, member 1 pseudogene	A pseudogene related to olfactory receptors in the nose
RPL7AP58	11p14.1	Ribosomal protein L7a pseudogene 58	A pseudogene conserved in ribosomes
SHISA9	16p13.12	Shisa homolog 9 (Xenopus laevis)	A transmembrane protein that associates with AMPA receptors in synaptic spines, and modulates short-term plasticity at excitatory synapses in the brain

Tab. 2c: The potential etiologic and functional role of genes associated with schizophrenia according to the genome-wide association studies

Gene	Location	Official Full Name	Function
NRG1	8p12	Neuregulin 1	A signalling protein that mediates cell-cell interactions and plays critical roles in the neuronal growth and development
AGBL1	15q25.3	ATP/GTP binding protein-like 1	A metallocarboxypeptidase mediating deglutamylation of target proteins
PDC	1q25.2	Phosducin	A phosphoprotein located in the retina, regulating visual phototransduction
PTGS2	1q25.2–q25.3	Prostaglandin-endoperoxide synthase 2 (prostaglandin G/H synthase and cyclo-oxygenase)	A key enzyme in prostaglandin biosynthesis involved in inflammation and mitogenesis
C1orf187	1p36.22	Chromosome 1 open reading frame 187	A protein (neucrin) predominantly expressed in developing neural tissues
AGTRAP	1p36.22	Angiotensin II receptor-associated protein	A transmembrane protein which negatively regulates angiotensin II signalling
MTIF3	13q12.2	Mitochondrial translational initiation factor 3	A translation initiation factor involved in mitochondrial protein synthesis
LNX2	13q12.2	Ligand of numb-protein X 2	A protein interacting with the NUMB protein, important in the development and plasticity of the nervous system
FTHL8	Xq28	Ferritin, heavy polypeptide 1 pseudogene 8	A pseudogene related to ferritin, the intracellular iron storage protein
AFF2	Xq28	AF4/FMR2 family, member 2	A transcriptional activator, its deficiency is associated with the Fragile X E syndrome (a mental retardation)
CCDC60	12q24.23	Coiled-coil domain containing 60	A protein involved in maintaining the proteinaceous structure
CSF2RA	Xp22.32 and Yp11.3	Colony stimulating factor 2 receptor, alpha, low-affinity (granulocyte-macrophage)	A subunit of a cytokine receptor
IL3RA	Xp22.3 or Yp11.3	Interleukin 3 receptor, alpha (low affinity)	A subunit of a cytokine receptor

Note: In the Tables 2a, 2b and 2c, the genes related to neurodevelopment and neuroplasticity are written in bold. Names of the genes in relation to immunology are in italics and the genes related to neuroendocrinology are underlined. The association studies for each gene can be found at http://www.schizophreniaforum.org (Schizophrenia Research Forum).