Article

A network view on Schizophrenia related genes

Sreedevi Chandrasekaran[1,2], Danail G. Bonchev[1-3]

[1]VCU Center for the Study of Biological Complexity, Richmond, VA, USA

[2]VCU School of Life Sciences, Richmond, VA, USA

[3]VCU Department of Mathematics and Applied Mathematics, Richmond, VA, USA

E-mail: dgbonchev@vcu.edu

Received 13 November 2011; *Accepted 17 December 2011*; *Published online 1March 2012*

IAEES

Abstract

This study is a part of a project investigating the molecular determinants of neurological diseases. To account for the systemic nature of these diseases we proceeded from a well established list of 38 schizophrenia-related genes (Allen et al., 2008; Ross et al., 2006) and investigated their closest network environment. The created networks were compared to recently proposed list of 173 schizophrenia related genes (Sun et al., 2009). 115 genes were predicted as potentially related to schizophrenia and subjected to GSEA. The enriched groups of proteins included neuromodulators, neurotransmitters and lipid transport. Over 100 signaling pathways were found significantly involved, signal transduction emerging as the most highly significant biological process. Next, we analyzed two microarray expression datasets derived from olfactory mucosa biopsies of schizophrenic patients and postmortem brain tissue samples from SMRIDB. The systems biology analysis resulted in a number of other genes predicted to be potentially related to schizophrenia, as well as in additional information of interest for elucidating molecular mechanisms of schizophrenia.

Keywords Schizophrenia; network analysis; microarray expression data.

1 Introduction

Schizophrenia is a severe, chronic and disabling mental disorder that affects about 1 percent of the human population worldwide. It is a complex disorder that has increasingly been recognized as a collection of different disorders including cognitive, social and emotional deficits. Previous studies suggests that there are lot of factors including heritability, genetic vulnerability, environmental influences, disruption in various neurotransmitter systems making schizophrenia a dynamic disorder leading to the deregulation of multiple pathways. Other mechanistic hypotheses have been related to immune system disorder, early neurodevelopmental interference, GABAergic, dopamine, and glutamatergic dysfunction. More recent molecular findings suggested that a complex interplay between receptors, kinases, proteins and hormones takes place in schizophrenia (Lang et al., 2007). Recently, pathway and gene network analysis (Ferrarini, 2011) were suggested to be a powerful tool in uncovering molecular mechanisms of complex disorder like schizophrenia (Jia et al., 2009; Sun et al., 2010; Rietkerk et al., 2009).

This study is the first part of a project investigating and comparing the molecular determinants of neurological diseases using gene network analysis. In order to account for the systemic nature of these diseases we proceeded from a well established "core" list of 38 schizophrenia-related genes/proteins (Allen et al., 2008; Ross et al., 2006), and investigated their closest network environment as a first step in defining the entire

space of such genes. The expanded set of genes were then compared to the recently published list of 173 genes potentially related to schizophrenia (Sun et al., 2009) and a number of new such genes were identified and subjected to Gene Set Enrichment Analysis (GSEA; Mootha et al. 2003; Subramanian et al. 2005). Next, we analyzed two microarray expression datasets (Matigian et al., 2010; Higgs et al., 2006). These datasets provided experimental validation of genes predicted by our systems biology approach. We thus utilized both computational and experimental datasets to generate new information of potential interest for the molecular mechanisms of the schizophrenia disorder.

2 Methods

2.1 Construction of networks

The latest version 8.0 of the Pathway Studio software (Ariadne Genomics, 2010) was applied to build several networks in which the core 38 selected proteins were connected either down the shortest paths between them or with proteins they target or with proteins which regulate them. A "new" set of potential schizophrenia-related genes was thus created from the closest environment of the 38 well-known schizophrenia-related genes. As shown in Fig. 1, this new set was then compared with the recently proposed extended list of 173 genes potentially related to schizophrenia (Sun et al., 2009). We ended up with a list of 115 predicted genes after discarding genes with local connectivity (node degree) less than three. These genes were then subjected to GSEA analysis.

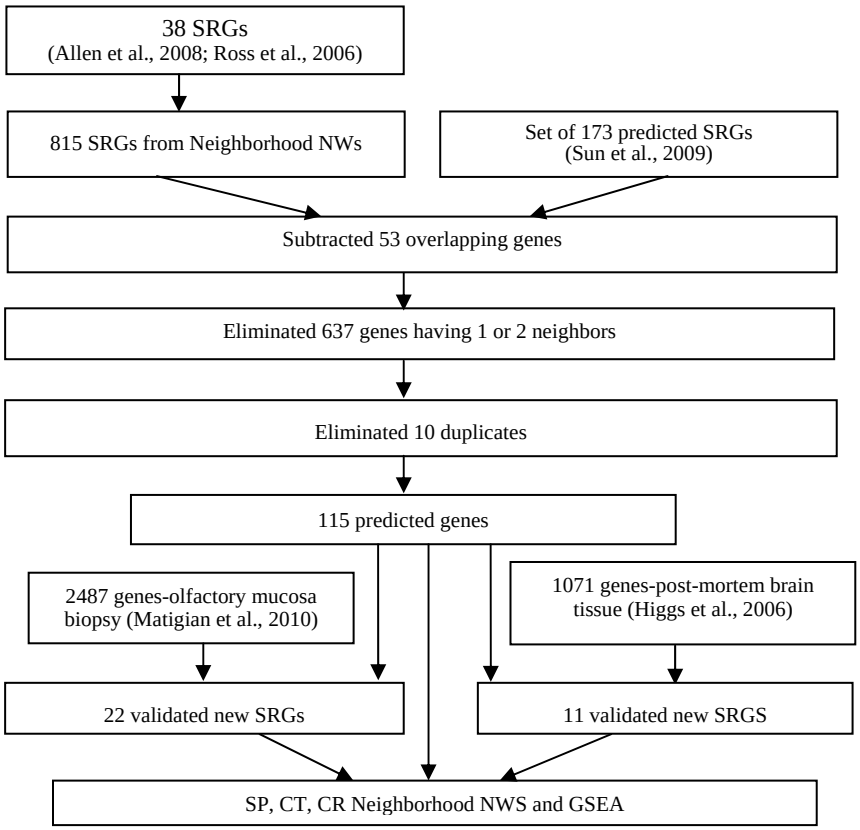

Fig. 1 The study workflow chart. SRGs - Schizophrenia-related genes; NWs - Networks

2.2 Microarray expression datasets

We utilized two publicly available microarray expression datasets to examine how well our 115 selected genes were experimentally represented. The first one was derived from olfactory mucosa biopsy samples (for more details see Matigian et al., 2010) and includes 42 samples from control, Schizophrenia and Parkinson subjects. For our analysis, we used the data of nine control and Schizophrenia subjects, matched by age and gender. The dataset was downloaded from the ArrayExpress database; accession number E-TABM-724. (http://www.ebi.ac.uk/arrayexpress)

The second microarray expression dataset was post-mortem brain tissue samples from The Stanley Medical Research – Online Genomics Database (SMRIDB) (https://www. stanleygenomics.org/) (Higgs et al., 2006). For our analysis, we used the expression dataset from Study ID: 5 (Investigator: Dobrin), from which we selected 20 age- and gender-matched samples of control and Schizophrenia subjects.

For both microarray expression datasets, we applied the latest version 8.0 of the Pathway Studio software, and investigated the gene expression patterns, and network environment. Enriched canonical pathways and biological functions were identified using Ingenuity Pathway Analysis (IPA version 9.0).

3 Results and Discussion

3.1 Prediction and ontology analysis of potential schizophrenia-related genes

As shown in the Workflow Chart (Fig. 1), 115 genes were predicted as potentially related to Schizophrenia. The close network environment of these genes was constructed and analyzed using Pathway Studio software version 8.0. Almost all of the 115 genes interact with each other directly. TP53, SRC, MAPK1, ESR1, EP300, STAT3, CAV1, CREB1, CASP3, and MAPK3 were the top 10 highly connected nodes in the shortest-path network. Different MAP kinases were found to be both highly targeted and regulators of other targets. Apart from the MAP kinases, SRC, EP300, CREB1, CASP3, and CEBPA were among the highly targeted genes, while SRC, CTNNB1, ESR1, STAT3, MAPT, PTK2, and CREB1 were major regulators.

The 115 genes were also subjected to GSEA analysis using Pathway Studio 8.0. The significantly enriched groups of proteins included among others neuromodulators and neurotransmitters, as well as lipid transport, known to be of importance in schizophrenia. Over 100 signaling pathways were found to be significantly involved, with the dominance of MAP kinases and other signaling pathways such as STAT, CTNNB, CEBPA/FOXO1A, FOXO/MYCN. Genes like CREB1, SHC1, RAF1, RPS6KA5, PLCG1, PIK3R1, were found in high frequency in the top 20 signaling pathways. Signal transduction emerged as the most highly significant biological process. Protein amino acid phosphorylation, response to glucocorticoid stimulus, sensory perception of pain and Ras protein signal transduction were some of the other schizophrenia-related significant biological process. Cellular components of high significance included among others axon, neuron projection, dendrite and dendrite cytoplasm, and presynaptic membrane.

3.2 Validation of the set of 115 predicted genes by the olfactory mucosa biopsy sample's data

Olfactory mucosa biopsy samples from nine age- and gender-matched control and Schizophrenia subjects were used (Matigian et al., 2010). The microarray expression dataset was analyzed using Pathway Studio 8.0. 2487 genes ($p<0.05$) were significantly differentially expressed between schizophrenia and control samples. The expression dataset was also subjected to the "Core analysis" and "Comparison analysis" of Ingenuity Pathway Analysis (IPA) software, version 9.0 (Ingenuity, 2010). 186 different molecular pathways were significantly altered in Schizophrenia, the top ten of which are shown in Table 1. It should be noted that the data in Table 1 differ considerably from those reported in (Matigian et al., 2010), where the old IPA version 6.0 has been used.

The 2487 significantly differentially expressed genes were compared with the 115 predicted gene list, finding 22 shared genes (ACHE, CAMK2A, CD4, CREB1, CTNNB1, EP300, FGF2, GNAS, GRM1, GRM5,

INS, MAPK1, NR3C1, OPRM1, PPM1A, PPP2CB, PRKACA, PTK2, RB1, SHC1, TGFB1, and YWHAE). Of these 22 genes, four encodes for transcription factors, protein kinase and receptor proteins each, three for ligands, two for phosphatases. All 22 genes except FGF2 directly interact with each other.

Table 1 Molecular signaling pathways significantly altered in microarray expression datasets

	Olfactory mucosa biopsy sample	**Post-mortem brain tissue sample**
Ingenuity Canonical Pathways	**p-value**	**p-value**
G-Protein Coupled Receptor Signaling[1]	< 0.001	0.0052
Axonal Guidance Signaling	< 0.001	< 0.001
Molecular Mechanisms of Cancer	< 0.001	< 0.001
Protein Kinase A Signaling	< 0.001	< 0.001
Role of Macrophages, Fibroblasts and Endothelial Cells in Rheumatoid Arthritis	< 0.001	< 0.001
Glucocorticoid Receptor Signaling[2]	0.0034	<0.001
Purine Metabolism[3]	0.0032	0.0013
Protein Ubiquitination Pathway[4]	insignificant	0.0389
Xenobiotic Metabolism Signaling[5]	0.0020	0.0263
Colorectal Cancer Metastasis Signaling	< 0.001	< 0.001

Pathways are selected statistically using Fisher's exact test (*p*- value). Refer [1]Bychkov et al., 2011; [2] Webster et al., 2002; [3] Yao et al., 2010; [4] Altar et al., 2005; [5] Gassó et al., 2010.

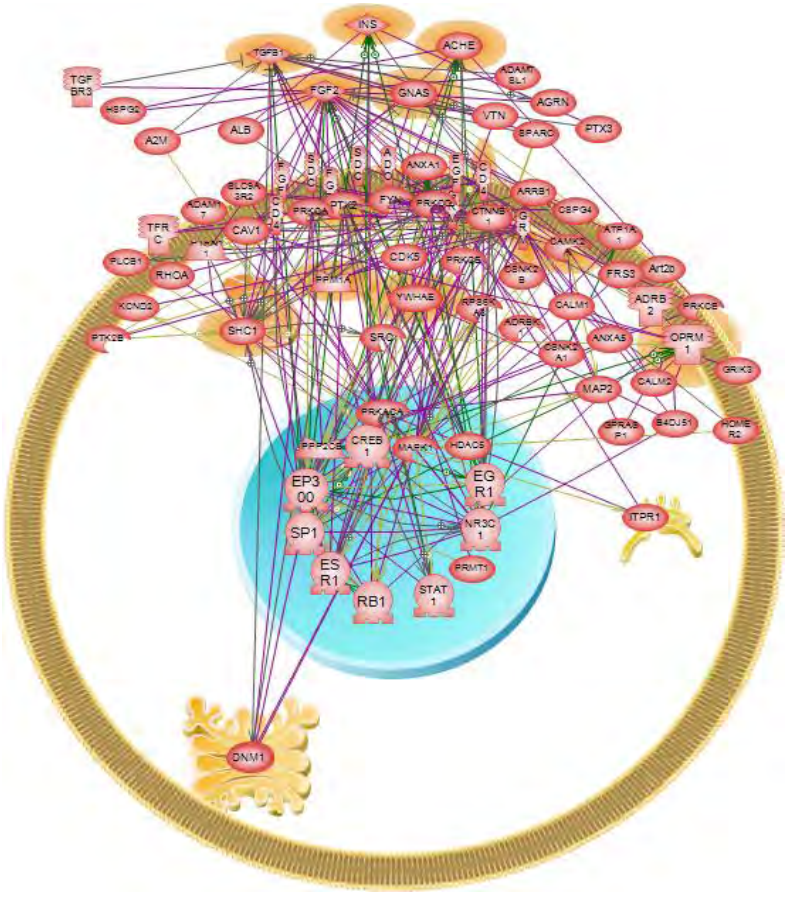

Fig. 2 The shortest-path network of 22 schizophrenia-related validated protein-encoding genes (highlighted in orange). The proteins are shown according to their location in the extracellular space, cell membrane, cytoplasm and nucleus. The protein-protein interactions are correspondingly: binding (167 interactions represented by purple solid line), direct regulation (46, gray solid line), promoter binding (26, green solid arrow), protein modification (74, yellow solid arrow).

Different close network environment like shortest-path, common target and common regulator networks were built and the results were analyzed. Genes like MAPK1, CTNNB1, FGF2, EP300, CREB1, SHC1, PTK2, GRM5, NR3C1, and ESR1 acts as major hubs in the shortest-path network (see Fig. 2). EP300, MAPK1, CREB1, NR3C1, and CTNNB1 are highly targeted nodes. CTNNB1, CREB1, EP300, PTK2, and RB1 were highly connected key regulators of schizophrenia-related genes. The local connectivity (node degree) values of the 22 validated genes in the four networks built are shown in the Table 2.

Two of the 22 validated genes (MAPK1, and NR3C1), which were found in our highly connected targets and regulators networks, were also implicated in other studies to have elevated expression in various mental disorder conditions like Schizophrenia, Bipolar disorder and Depression (Webster et al., 2002; Kyosseva et al., 1999). Like other previous studies, our data also showed altered expression of ACHE, CAMK2A, CD4, FGFR, GNAS, GRM1, GRM5, OPRM1 and YWHAE, suggesting immunological abnormalities (Cazzullo et al., 1998), possible use of ACHE inhibitors in improving cognitive impairment (Stip et al., 2007), altered expression of many neuroreceptors (Novak et al., 2006), corticostriatal plasticity and antagonizing the signaling pathway of dopamine receptors (Terwisscha van Scheltinga et al., 2010), alterations in intracellular G-protein signaling (Minoretti et al., 2006) and in glutamate receptors (Raw et al., 2010), modulation in neurotransmitters response (Devon et al., 2001), and various neurodevelopmental abnormities (Serý et al., 2010; Ikeda et al., 2008) in Schizophrenia subjects.

Table 2 Local connectivity (node degree) of the 22 Schizophrenia-related validated genes in different Pathway Studio networks

Name	Codes for	DI	SP	CT	CR
ACHE	Protein	1	8	1	6
CAMK2A	Protein kinase	3	8	10	4
CD4	Receptor	4	8	7	9
CREB1	Transcription Factor	14	25	93	39
CTNNB1	Protein	7	32	38	54
EP300	Transcription Factor	11	29	122	38
FGF2	Ligands	0	31	0	5
GNAS	Protein	1	10	1	9
GRM1	Receptor	1	14	2	5
GRM5	Receptor	1	19	4	2
INS	Ligands	4	7	5	15
MAPK1	Protein kinase	10	37	101	31
NR3C1	Transcription Factor	9	19	47	27
OPRM1	Receptor	1	11	1	10
PPM1A	Phosphatase	1	4	8	0
PPP2CB	Phosphatase	2	8	11	4
PRKACA	Protein kinase	2	11	3	0
PTK2	Protein kinase	4	21	14	37
RB1	Transcription Factor	5	10	31	35
SHC1	Protein	4	25	8	31
TGFB1	Ligands	2	15	3	14
YWHAE	Protein	1	5	4	2

DI – Direct interaction; SP – Shortest-path; CT – Common targets; CR – Common regulators networks

The 22 validated genes were also subjected to the "core analysis" of the IPA 9.0 software. Many molecular pathways were found to be significantly altered in Schizophrenia, including CREB Signaling in Neurons, Synaptic Long Term Potentiation pathway, and PPARa/RXRa Activation.

3.3 Validation of the set of 115 predicted genes by the post-mortem brain tissue sample's data

We used 20 age- and gender- matched control Schizophrenia post-mortem brain tissue samples (Higgs et al., 2006). The microarray expression dataset was analyzed using Pathway Studio 8.0, finding 1071 gene expression significantly ($p<0.05$) modulated in schizophrenia compared to control samples. The expression dataset was also subjected to the "Core analysis" and "Comparison analysis" of the IPA 9.0 software. Nearly 180 different molecular pathways were significantly altered in Schizophrenia; the top ten are shown in the Table 1. Eleven from those 1071 genes were shared with the 115 genes predicted in Section 3.1 (See Table 1).

Different close network environments of the 11 shared genes were used to build expanded networks by connecting them along the shortest possible paths with involvement of additional connecting proteins, as well as connecting them to their common regulators or their common targets. In the shortest path network (See Fig. 3) all 11 genes were connected to each other, with ESR1, GSK3B, MAPK8, PPM1A, and CREB1 genes acting as major hubs. CREB1, MAPK8, ESR1, GSK3B, and PGR were both highly targeted and highly involved in regulation of other genes. The local connectivities (node degrees) of the 11 gene's in the created four networks are shown in the Table 3.

Table 3 Local connectivity (node degree) of the 11 Schizophrenia-related validated genes in different Pathway Studio networks

Name	Codes for	DI	SP	CT	CR
CANX	Protein	1	3	3	1
CREB1	Transcription Factor	8	18	54	22
ESR1	Transcription Factor	7	24	46	27
GNAQ	Protein	0	3	0	1
GSK3B	Protein kinase	4	22	42	16
MAPK8	Protein kinase	3	21	47	9
NCK1	Protein	0	5	2	4
PGR	Transcription Factor	4	8	16	20
PPM1A	Phosphatase	0	21	9	0
PPP2CB	Phosphatase	1	7	6	2
TGFBR1	Receptor	0	13	5	4

DI – Direct interaction; SP – Shortest-path; CT – Common targets; CR – Common regulators networks

The GSK3B protein, recently related to schizophrenia (Lovestone et al., 2007; Souza et al., 2008), was identified as a major hub of transcription factors regulation. CREB protein stimulates the expression of a number of genes. Also, any alterations in CREB expression may be associated with schizophrenia, including the regulation of dopamin (Kawanishi et al., 1999). Previous studies show that variations in the ESR1 gene are associated with schizophrenia (Weickert et al., 2008).

The 11 validated genes were also subjected to the "core analysis" of IPA 9.0 software. Many molecular pathways were significantly altered in the examined Schizophrenia post mortem samples, with Cardiac Hypertrophy Signaling being heavily altered, followed by typical schizophrenia-involved pathways like Glucocorticoid Receptor Signaling, Wnt/b-catenin Signaling, and ILK Signaling.

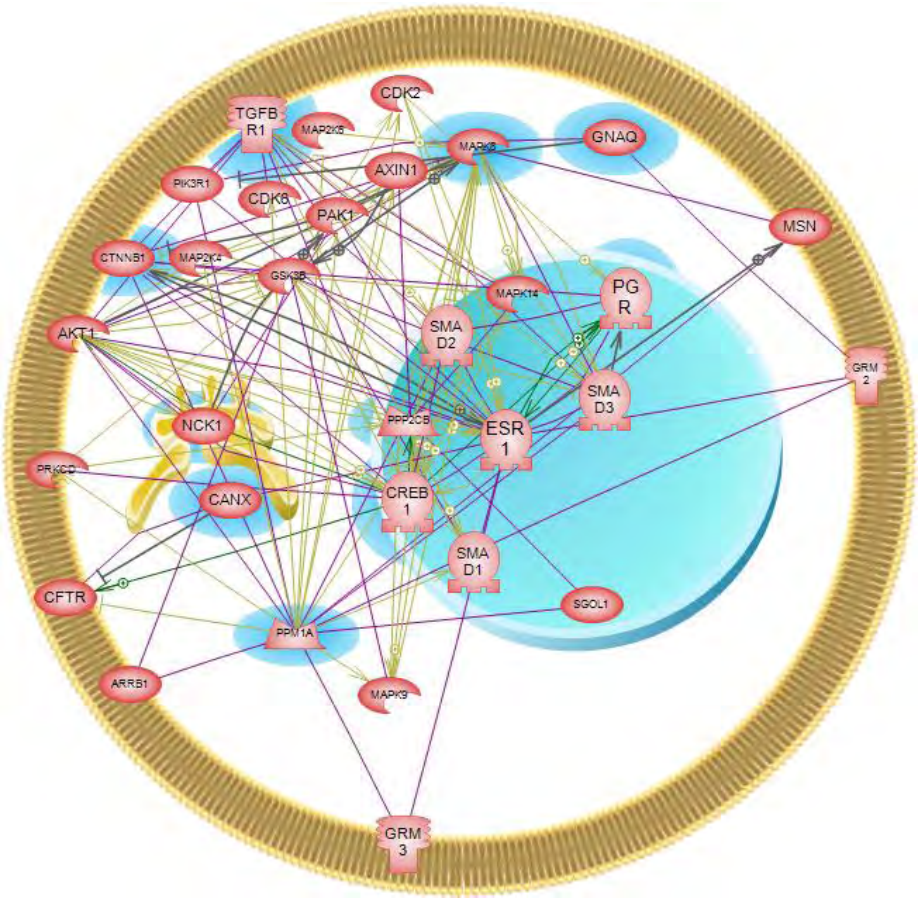

Fig. 3 Eleven Schizophrenia-related validated gene's shortest-path network. The protein-protein interactions shown are: binding (55 interactions represented by purple line), direct regulation (11, gray line), promoter binding (6, green arrow), protein modification (59, yellow arrow). All 11 Validated genes (highlighted in blue) are connected.

The most highly altered molecular and cellular functions included the reproductive System, with reproductive hormones possibly contributing to the onset of schizophrenia (Stevens et al., 2002), while another link being the extremely low fertility of schizophrenia subjects (Ritsner et al., 1992). Endocrine system, known to malfunction in schizophrenia both centrally and peripherally was found to be the next highly modulated system (Riecher-Rössler et al., 1993).

3.4 Concluding analysis

We found 157 genes that were significantly differentially expressed in both olfactory mucosa sample and post-mortem brain tissue samples. Three of those genes, namely CREB1, PPM1A, and PPP2CB, were also found in most of our network-based datasets and may be expected to belong to an essential part of the molecular mechanisms of schizophrenia. Although not included in the list of 38 basic schizophrenia-related genes (Allen et al., 2008, Ross et al., 2006), they all have been previously associated with schizophrenia. CREB1 was briefly discussed in the previous subsection, PPM1A is considered potential therapeutic agent for the prevention or treatment of schizophrenia (Bahn et al., 2006), and PPP2CB has also been briefly related to it (Marvanova et al., 2004). However, we identified five genes (GNAQ, NCK1, PGR, SHC1, and TGFBR1) for which no previously reported relation to schizophrenia was found.

Ten genes (ADRB2, ARRB1, CAV1, CD44, CDK5, DNM1, ESR1, FYN, PRKCB, and SRC) from the 115 schizophrenia-related ones predicted in Section 3.1 emerged also in the shortest-path network built for the 22 validated genes. Similarly, three from the 115 predicted genes (ARRB1, MAPK14, and MAPK9) were found included in the shortest-path network built for the 11 validated genes. Two other predicted genes (CD44 and PRKCB) have not yet being related to Schizophrenia. Our systems biology approach thus expanded the pool of genes potentially related to schizophrenia, as a basis for further efforts to elucidate the molecular and cellular mechanisms of Schizophrenia.

Irrespective of their very different nature, the two microarray expression analyses identified the same molecular pathways that were the most deregulated in patients samples. They all have been implicated in Schizophrenia, to mention few of them: G-Protein Coupled Receptor Signaling, Glucocorticoid Receptor Signaling, Purine Metabolism, Protein Ubiquitination Pathway, Xenobiotic Metabolism Signaling, and Cardiac Hypertrophy Signaling (Bychkov et al., 2011; Webster et al., 2002; Yao et al., 2010; Altar et al., 2005; Gassó et al., 2010].

The detailed information on schizophrenia related genes and cellular processes provided by our study indicates the potential of the systems biology approach when applied as shown in Fig. 1 to an expanded space of disease genes. This expansion of the seed sets of genes found from literature search and microarray analysis was performed by using their immediate network environment of various regulatory, binding and other interactions. Such an integrative process offers better chances to identify the key players in the disease, and to offer ways to suppress them.

References

Allen NC, Bagade S, McQueen MB, et al. 2008. Systematic meta-analyses and field synopsis of genetic association studies in schizophrenia: the SzGene database. Nature Genetics, 40(7): 827-34

Altar AC, Jurata LW, Charles V, et al. 2005. Deficient hippocampal neuron expression of proteasome, ubiquitin, and mitochondrial genes in multiple Schizophrenia cohorts. Biological Psychiatry, 58(2): 85-96.

Ariadne Genomics, Pathway Studio, version 8.0, 2010, http://www.ariadnegenomics.com.

Bahn S, Ryan M, Huffaker S. 2006. Differential gene expression in schizophrenia. US Patent 2006/0150264 A1

Bychkov ER, Ahmed MR, Gurevich VV, et al. 2011. Reduced expression of G protein-coupled receptor kinases in schizophrenia but not in schizoaffective disorder. Neurobiology of Disease, 44(2): 248-258

Cazzullo CL, Saresella M, Roda K, et al.1998. Increased levels of CD8+ and CD4+ 45RA+ lymphocytes in schizophrenic patients. Schizophrenia Research, 31(1): 49-55

Devon RS, Anderson S, Teague PW, et al. 2001. The genomic organisation of the metabotropic glutamate receptor subtype 5 gene, and its association with schizophrenia. Molecular Psychiatry, 6(3): 311-314

Ferrarini A, 2011. Some thoughts on the control of network systems. Network Biology, 1(3-4): 186-188

Gassó P, Mas S, Alvarez S, et al. 2010. Xenobiotic metabolizing and transporter genes: gene-gene interactions in schizophrenia and related disorders. Pharmacogenomics, 11(12): 1725-1731

Higgs BW, Elashoff M, Richman S, et al. 2006. An online database for brain disease research. BMC Genomics, 7(4):70

http://www.ebi.ac.uk/arrayexpress

https://www. stanleygenomics.org

Ikeda M, Hikita T, Taya S, Uraguchi-Asaki J, et al. 2008. Identification of YWHAE, a gene encoding 14-3-3epsilon, as a possible susceptibility gene for schizophrenia. Human Molecular Genetics, 17(20): 3212-3222

Ingenuity Systems, IPA version 9.0, 2010. www.ingenuity.com.

Jia P, Sun J, Han L, Zhao Z. 2009. Pathway and Network Analysis of Schizophrenia Candidate Genes under Meta-Analysis Linkage Peaks. In: Bioinformatics, Systems Biology and Intelligent Computing, IJCBS 2009. International Joint Conference, 442-447

Kawanishi Y, Harada S, Tachikawa H, et al. 1999. Novel variants in the promoter region of the CREB gene in schizophrenic patients. Journal of Human Genetics, 44(6): 428-430

Kyosseva SV, Elbein AD, Griffin WS, et al. 1999. Mitogen-activated protein kinases in schizophrenia. Biological Psychiatry, 46(5): 689-696

Lang UE, Puls I, Muller DJ, Strutz-Seebohm N, Gallinat J. 2007. Molecular mechanisms of schizophrenia. Cellular Physiology and Biochemistry, 20(6): 687-702

Lovestone S, Killick R, Di Forti M, et al. 2007. Schizophrenia as a GSK-3 dysregulation disorder. Trends in Neuroscience, 30(4): 142-149

Marvanova M, Lakso M, Wong G. 2004. Identification of genes regulated by memantine and MK-801in adult rat brain by cDNA microarray analysis. Neuropsychopharmacology, 29(6): 1070-1079

Matigian N, Abrahamsen G, Sutharsan R, et al. 2010. Disease-specific, neurosphere-derived cells as models for brain disorders. Disease Models and Mechanisms, 3(11-12): 785-798

Minoretti P, Politi P, Coen E, et al. 2006. The T393C polymorphism of the GNAS1 gene is associated with deficit schizophrenia in an Italian population sample. Neuroscience Letters, 397(1-2): 159-163

Mootha VK, Lindgren CM, Eriksson KF et al. 2003. PGC-1alpha-responsive genes involved in oxidative phosphorylation are coordinately downregulated in human diabetes. Nature Genetics, 34(3): 267-273

Novak G, Seeman P, Tallerico T. 2006. Increased expression of calcium/calmodulin-dependent protein kinase IIbeta in frontal cortex in schizophrenia and depression. Synapse, 59(1): 61-68

Ross CA, Margolis RL, Reading SA, et al. 2006. Neurobiology of schizophrenia. Neuron, 52(1): 139-153

Raw F, McRae AF, Pocklington AJ, et al. 2010. Clustered coding variants in the glutamate receptor complexes of individuals with schizophrenia and bipolar disorder. PLoS ONE, 6(4): e19011

Riecher-Rössler A, Häfner H. 1993. Schizophrenia and oestrogens — is there an association? European Archives of Psychiatry and Clinical Neuroscience, 242(6): 323-328

Rietkerk T, Boks MPM, Sommer IEC, et al. 2009. Network analysis of positional candidate genes of schizophrenia highlights myelin-related pathways. Molecular Psychiatry, 14(4): 353–355

Ritsner M, Sherina O, Ginath Y. 1992. Genetic epidemiological study of schizophrenia: reproduction behaviour. Acta Psychiatrica Scandinavica, 85(6): 423-429

Serý O, Prikryl R, Castulík L, St'astný F. 2010. A118G polymorphism of OPRM1 gene is associated with schizophrenia. Journal of Molecular Neuroscience, 41(1): 219-222

Souza RP, Romano-Silva MA, Lieberman JA, et al. 2008. Association study of GSK3 gene polymorphisms with schizophrenia and clozapine response. Psychopharmacology, 200(2): 177-186

Stevens JR. 2002. Schizophrenia: Reproductive Hormones and the Brain. American Journal of Psychiatry, 159(5):713-719

Stip E, Sepehry AA, Chouinard S. 2007. Add-on therapy with acetylcholinesterase inhibitors for memory dysfunction in schizophrenia: a systematic quantitative review, part 2. ClinNeuropharmacology, 30(4): 218-229.

Subramanian A, Pablo T, Vamsi KM et al., 2005. Application of a priori established gene sets to discover biologically important differential expression in microarray data. Proceedings of the National Academy of Science of USA, 102(43): 15278-15279

Sun J, Jia P, Fanous AH, et al. 2009. A multi-dimensional evidence-based candidate gene prioritization approach for complex diseases-schizophrenia as a case. Bioinformatics, 25(19): 2595-6602

Sun J, Jia P, Fanous AH, et al. 2010. Schizophrenia gene networks and pathways and their applications for novel candidate gene selection. PLoS ONE, 5(6): e11351

Terwisscha van Scheltinga AF, Bakker SC, Kahn RS. 2010. Fibroblast Growth Factors in Schizophrenia. Schizophrenia Bulletin, 36(6): 1157-1166

Webster MJ, Knable MB, O'Grady J, et al. 2002. Regional specificity of brain glucocorticoid receptor mRNA alterations in subjects with schizophrenia and mood disorders. Molecular Psychiatry, 7(9): 985-994

Weickert CS, Miranda-Angulo AL, Wong J, et al. 2008. Variants in the estrogen receptor alpha gene and its mRNA contribute to risk for schizophrenia. Human Molecular Genetics, 17(15): 2293–2309

Yao JK, Dougherty GG Jr., Reddy RD, et al. 2010. Homeostatic imbalance of purine catabolism in first-episode neuroleptic-naïve patients with schizophrenia. PLoS ONE, 5(3): e9508