

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

185,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Genetics and Epigenetics of Schizophrenia

Esmaeil Shahsavand Ananloo

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.75930>

Abstract

Schizophrenia (SCZ) is a complex mental disorder, with a longstanding history of neurobiological investigation. It is more common in those persons who are genetically predisposed to the disorder. Since Kraepelin, psychiatrists were aware that the SCZ tended to run in families. Its heritability is up to 85%. Although the etiology of SCZ is unknown, it is now thought to be multifactorial, with multiple susceptibility genes interacting with environmental and developmental factors. There is a huge amount of genetic studies, including polymorphisms, expression, methylation, microRNAs, and epigenomics. However, identifying genes for SCZ using traditional genetic approaches has thus far proven quite difficult. Reasons for this include the complexity, heterogeneity, and comorbidity of this disorder, and also the poor definition of the clinical phenotype. Important approaches to find the relation between genotype and phenotype and may be causal genetic factors are endophenotypes and pathway analysis. However, genetic researchers need to consider carefully the models of causality they choose. There is a pathophysiological pathway that extends from genes, through proteins, neurons, neural circuits, neural regions, mental functions, external behaviors, and symptoms of SCZ. In this chapter, the genetics and epigenetics of SCZ are briefly discussed.

Keywords: schizophrenia, genetic, epigenetic, etiology, pathophysiology, endophenotype, pathway analysis

1. Introduction

Schizophrenia is a serious, disabling, and complex mental disorder, with a longstanding history of neurobiological investigation [1]. It may be one of the most disabling disorders known to human. Schizophrenia can affect anyone at any point in his or her life. It is more common in those persons who are genetically predisposed to the disorder. The first psychotic episode generally occurs in late adolescence or early adulthood and often appears earlier in

men than in women. Schizophrenia, as a common disorder, has a worldwide prevalence of around 0.3–1.0% [2]. Clinically, it is characterized by a combination of positive and negative symptoms, cognitive impairments, and disorganized behaviors.

There are 130,024 citations (110,613 papers, 17,847 reviews, and 1564 meta-analysis) related to “schizophrenia,” 12,038 citations (9666 papers, 2134 reviews, and 238 meta-analysis) related to “schizophrenia gene,” 1317 citations (1060 papers, 178 reviews, and 79 meta-analysis) related to “schizophrenia genome-wide association study,” and 234 citations (216 papers, 11 reviews, and 7 meta-analysis) related to “schizophrenia gene enrichment” in PubMed (accessed on January 29, 2018).

Since Kraepelin delineated the disorder dementia praecox in 1899, psychiatrists were aware that the SCZ tended to run in families. Until now, there are several family studies in SCZ [3, 4]. While, the probability of developing SCZ in general population is 1%, the probability of its developing as the offspring of one parent with the disorder is approximately 17%, and the offspring of both parents with the disorder is approximately 46% [5].

A vulnerability-stress model, in which SCZ is thought to be multifactorial, with multiple susceptibility genes interacting with environmental and developmental factors. For example, the immune response to a wide variety of bacterial or viral pathogens may be the link between pre-natal infection and postnatal brain pathologies, including SCZ [6]. Additionally, intrauterine or postnatal complications with a negative impact on fetal brain development, nutritional deficiencies with effects on neurotransmitter systems, or maternal exposure to stressors are among the other important factors [7]. Identifying genes for psychiatric disorders using traditional genetic approaches has thus far proven quite difficult. Reasons for this include the complexity, heterogeneity, and comorbidity of these disorders and also the poor definition of the clinical phenotype [8]. Different studies, including MicroRNAs [9, 10], genetic polymorphisms [11, 12], gene expression [13, 14], methylation [15], and epigenomics [16, 17] are the most important genetic studies in SCZ.

2. Genetics of schizophrenia

2.1. An overview

Evidence including genetic findings shows that the early neurodevelopmental events have been implicated in the pathogenesis of disorder (**Table 1**) [1]. Traditionally, the most genetic researches on SCZ have concentrated on chromosomes and genes. These include cytogenetics, linkage, association, gene expression, and whole genome and exome scans. Although these studies have identified a number of genomic regions of interest, these have not produced any confirmed causations.

There are reasons as to why genetic approaches have met with little success in SCZ. First is that, there are no specific biological markers. Diagnostic systems, including diagnostic and statistical manuals of mental disorders (DSMs) and international classifications of diseases (ICDs), are categorical classifications and are based on interview and self-reporting of the patients. So, they are not optimal in genetic research on complex disorders. Second is the problem of

Traditional structural genetic studies	Newer structural genetic studies	Traditional functional genetic studies (gene encoding studies)	Newer functional genetic studies	Epigenetic studies
Cytogenetic studies	Genome-wide association studies (GWASs)	mRNA studies	microRNA studies	DNA modification studies
Linkage studies	Whole exome studies	Protein studies	Long noncoding RNA studies	Histone modification studies
Candidate gene association studies			Other noncoding RNA studies	
			Genome-wide expression studies	

Table 1. An overview to the genetic and epigenetic studies of schizophrenia.

genotype-phenotype relationship. After a century ago, when Wilhelm Johannsen proposed the terms “genotype” and “phenotype,” our knowledge about the genetics, phenotype, and the concept of causality has evolved dramatically [18]. For example, genotype heterogeneity means that there are many genotypes that produce the same phenotype. In addition, phenotype heterogeneity means that the same genotype may produce different phenotypes. The alternate approach to find the relationship between genotype and phenotype may be endophenotypes that will be useful in detecting genes contributing to SCZ [19, 20]. However, the studies of endophenotypes (characteristics that are intermediate between the genotype and a phenotype of interest) associated with SCZ are not yet enough. Another approach may be the path analysis to identify causal variables that produce phenotypes [21, 22]. However, the chosen models of causality are very important [18]. Third is the genetic hypothesis being tested. The problems are the number of gene variants involved, the heterogeneous mechanism of the disorder, and the understanding of their interactions with the environmental and developmental factors to predisposition to SCZ. So, there is a long pathophysiological chain that extends from genes, through proteins, neurons, neural circuits, neural pools, neural regions, mental functions, external behaviors, and symptoms construct of SCZ.

By using high-throughput technologies, a huge amount of studies, including genome-wide association studies (GWASs) have reported that genetic variants, such as copy number variations (CNVs) or single nucleotide polymorphisms (SNPs) play significant roles in the pathogenesis of SCZ. In recent years, and based on the emergence of international consortia to achieve larger sample sizes, clinical, and statistically expertise and also replicable genetic findings [23], our understanding of the genetic architecture of SCZ, the number of risk variants, and their frequencies and effect sizes have been transformed. Genome-wide association studies of genetic variants have approximately tripled the number of candidate genetic loci [24]. The Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC) used GWAS arrays to identify 128 independent associations spanning 108 regions. These findings demonstrate the involvement of biological processes of the brain. For example, there are associations among gene expression patterns in tissues with some roles in the immune system, providing support for the link between the immune system and SCZ [23].

2.2. Heritability

The heritability is a statistic that estimates the degree of variation in a phenotypic trait or disorder in a population that is due to genetic variation between individuals [25]. Schizophrenia is highly heritable [26] and its genetic architecture is complex and heterogeneous. Its heritability has been estimated from 81% [26] up to 85% [27], showing a non-Mendelian inheritance pattern [28]. Reported concordance rate of SCZ in monozygotic twins is about 50%; from 41–65% [27, 29], while siblings and dizygotic twins show proband concordance rates as high as 28% [27]. The risk of the general population developing the SCZ is about 0.3–1.0% worldwide [2, 30].

Evidence shows the heritability of different aspects of SCZ, such as brain region volumes [31, 32] and cognitive disabilities [33]. Thus, the combination of genetics and brain imaging (imaging-genetics approach) will be a useful strategy to assess the effects of risk genetic variants on anatomical and functional connectivities [32]. For example, the heritability in subcortical and limbic volumes ranged from 0.45 in the right hippocampus to 0.84 in the left putamen [31]. General cognitive disabilities in SCZ have also genetic contributors. By using the genome-wide complex-trait analysis (GCTA) approach, to estimate the total heritability captured by common DNA markers on genotyping arrays [34], it was shown that individuals at ultra-high risk for the disorder, relatives of the patients with SCZ spectrum disorders, and children with antecedents of SCZ may have cognitive impairments as well [33].

2.3. Candidate gene association studies

The candidate gene association study has been a major approach to discover the causative genetic factors of complex traits or disorders. Prior to the GWAS era, candidate studies were a major approach in SCZ genetics [35] and have been a pioneer in the field of genetic association studies to identify risk genetic variants associated with a particular trait or disorder [36]. These studies, including case-control and family studies, directly test the effects of genetic variants, usually CNVs or SNPs of potentially contributing genes. The candidate gene studies are relatively cheap and quick to perform, but are limited by how much is known about the biology of the disorder being investigated [37]. With the advent of rapidly changing technology, there has been an explosion of *in silico* tools available to researchers, giving them fast, efficient resources, and reliable strategies to find casual genetic variants for candidate study or GWAS [36]. Population stratification is also a major confounding factor for population-based case-control association studies and can result in false positive associations [38]. This may be solved by considering a replication study using an independent and random cohort of test and control populations or through a family study. These approaches may reduce the chance of occurrence of a similar admixture showing similar patterns of variations [39]. Prior to the advances brought about by the Human Genome Project [40], the International HapMap Project [41], and then, 1000 Genomes Project [42], it was difficult and expensive to genotype a comprehensive list of genetic variants in a genomic region. Investigators thus tended to genotype a few genetic markers in a candidate gene selected based on prevailing theories of the etiopathology of SCZ or positional candidate genes from linkage or cytogenetic studies.

The more popular hypothesis, the common disease—common variant hypothesis suggests that SCZ is associated primarily with common genetic variants [43]. Based on this hypothesis,

most of the genetic association studies have focused on these variations in SCZ. This hypothesis constitutes the rationale of GWASs, in which millions of variants, including SNPs were assessed in thousands of individuals [44, 45]. Copy number variations are sections of the genome that are repeated and the number of repeats in the genome varies between individuals [46]. Structural variations of DNA, such as CNVs, have contribution to normal genomic variability and to risk for human diseases [47]. Many studies have demonstrated that CNVs play important roles in susceptibility to SCZ [47–49].

The SZGene database (obtained 11/2017) listed 1727 candidate gene papers investigating over 1008 genes and 8788 polymorphisms. Based on published genetic association studies of SCZ, it has been reported that across 118 meta-analyses, 16 genes, including *APOE*, *COMT*, *DAO*, *DRD1*, *DRD2*, *DRD4*, *DTNBP1*, *GABRB2*, *GRIN2B*, *HP*, *IL1B*, *MTHFR*, *PLXNA2*, *SLC6A4*, *TP53*, and *TPH1* showed significant effects [50]. By using a translational convergent functional genomics approach, using candidate genetic studies, and a poly evidence scoring and pathway analyses, many genes, including *DISC1*, *TCF4*, *MBP*, *MOBP*, *NCAM1*, *NRCAM*, *NDUFV2*, *RAB18*, *ADCYAP1*, *BDNF*, *CNR1*, *COMT*, *DRD2*, *DTNBP1*, *GAD1*, *GRIA1*, *GRIN2B*, *HTR2A*, *NRG1*, *RELN*, *SNAP-25*, *TNIF*, and a few top genes, including *DISC1*, *HSPA1B*, *MBP*, and *TCF4* were identified [51]. Across meta-analyses, candidate genes, including *APOE*, *COMT*, *DAO*, *DRD1*, *DRD2*, *DRD4*, *DTNBP1*, *GABRB2*, *GRIN2B*, *HP*, *IL1B*, *MTHFR*, *PLXNA2*, *SLC6A4*, *TP53*, *TPH1*, *RELN*, *MnSOD*, *GSTM1*, *ZNF804A*, *CACNA1C*, *ANKK3*, *BDNF*, *GRIN3A*, *FAAH*, *DNMT1*, *MYO18B*, *CFB*, *GRM7*, *GRM8*, *miR-137*, *MPC2*, and *CSMD1* showed nominally significant effects [11, 50, 52]. However, some of them have been questioned [35, 53–55]. A likely reason why candidate gene studies did not achieve their primary aims is inadequate statistical power. However, the considerable efforts embodied in early studies unquestionably set the stage for current successes in genomic approaches to SCZ [35].

2.4. Genome-wide association studies

A GWAS or whole genome association study (WGAS) is an approach that involves rapidly scanning genetic variants across the genomes of many people to find variations associated with a particular trait or disease. By using this approach, researchers can use the information to develop better hypotheses to detect, treat, and prevent the diseases. Such studies are particularly useful in finding genetic variations that contribute to mental disorders. Genome-wide association study searches the genome for a genome-wide set of genetic variants in different individuals to see if any variant is associated with a normal trait or a disease. This is a hypothesis-free strategy, and typically searches the genome for SNPs, or CNVs that occur more frequently in people with a particular disease than in people without the disease. Genome-wide significance is $P < 5.0 \times 10^{-8}$. Meta-analyses of GWAS data have begun to lead to promising new discoveries for SCZ [56]. Within the last few years, large-scale GWASs of SCZ have identified multiple risk variants with significant association with the disorder. However, these variants could explain only a small proportion of the heritability of SCZ and their effect sizes are relatively small, suggesting that more risk variants may be detected when increasing sample size in analysis [57, 58].

By the analysis of an European ancestry sample GWAS and then through a replication study, Ripke et al. [45] found significant associations for seven loci, including 1p21.3, 2q32.3, 6p21.32-p22.1, 8p23.2, 8q21.3, 10q24.32-q24.33, and 18q21.2 with SCZ. The strongest finding was with a

miRNA-137 SNP, a known regulator of neuronal development. In a meta-analysis of 18 GWASs and a replication study, Aberg et al. [3] found significant effect with SCZ for *TCF4*, *NOTCH4*, *POM121L2*, *AS3MT*, *CNNM2*, and *NT5C2* genes. By carrying out a GWAS meta-analysis, Sleiman et al. [59] found 40 SNPs in six significant loci, including *SDCCAG8*, *ITIH1*, major histocompatibility complex (*MHC*), *MAD1L1*, *CSMD1*, and *TSNARE1* genes. By analyzing two genome-wide association data sets of European-American patients with SCZ, significant associations between negative symptoms of SCZ and *BCL9*, *TMEM245*, *RNF144B*, *CTNNA3*, and *ZNF385D* genes have been detected [60]. The largest published GWAS meta-analysis of SCZ is of 34,000 patients in a meta-analysis of 52 GWASs from the Psychiatric Genomics Consortium (PGC) which identified 108 genome-wide significant loci [61]. Through large GWAS, an intronic SNP within *CSMD1* gene, rs10503253, one of the top risk SNPs for SCZ in Europeans discovered [11]. It may be concluded that the risk “A” allele is relevant to brain structure and neurocognitive functioning and these effects may be a part of the mechanism by which the *CSMD1* mediates risk for SCZ [62, 63]. By combining two SCZ cohort studies, Luo et al. [58] reported a genome-wide significant risk locus at 22q13.1. In their meta-analysis, seven SNPs on chromosome 22q13.1 reached the genome-wide significant effect, and most significant association was with SNP rs6001946 ($P = 2.04 \times 10^{-8}$). All seven SNPs are located in the *MKL1* gene.

It has been reported that a rare risk variation at *AKAP9* and a protective variation at *NRXN1* are in susceptibility to SCZ [64]. By doing a meta-analysis of data from the PGC and additional SCZ family sample, SNP rs4765905 in *CACNA1C* showed a strong effect [65]. Through the meta-analysis of a UK case/control study and GWAS data from the PGC, a significant effect of two *SLC30A3* gene SNPs (rs11126936 and rs11126929) was found in female subjects [66]. Chang et al. [67] in a GWAS study in Europeans (but not in Asians) found a significant effect with SCZ for *VRK2* gene SNP rs2312147. In their GWAS meta-analysis, it has been reported that rs10489202 in *MPC2* gene is significantly associated with SCZ in Han Chinese samples [68].

2.5. Gene expression studies

2.5.1. Gene encoding studies

It has been postulated that the underlying neuropathology of SCZ, at least, resides in the periodic activation of a defective genes, as a progressive process [69]. Changes in gene expression in brains of patients with SCZ have been hypothesized to reflect possible pathways related to its pathophysiology [70]. Progressive cortical reorganization and gray matter abnormalities may be pathophysiological processes in disorder [71, 72]. These changes are in parallel with changes in symptoms and cognitive impairments [73]. Epidemiological evidence suggests the widespread gene-environment interactions in the etiology of SCZ [74, 75]. So, it may be hypothesized that these interactions can alter the gene expression pattern in the brain of patients. By using the Gene Expression Omnibus Database, Karim et al. [76] showed a total of 527 differentially expressed genes of which 314 are up regulated and 213 are down regulated.

There are differences in pathophysiology of SCZ between male and female patients. It seems that the pattern of genetic architecture is different between two sexes. For example, the upregulation of 59 genes and downregulation of other 105 genes in the peripheral blood mononuclear

cells (PBMCs) from patients with SCZ have been reported [77]. By using the PBMC samples, a genome-wide expression analysis showed the alterations of gene expressions, such as *MEF2D*, *S100A12*, and *AKT1*, with immune system function [77, 78]. Additionally, in their meta-analysis, Qin et al. [13] tested for a sex by diagnosis interaction on gene expression. These authors reported that 23 genes were up regulated and 23 genes were down regulated significantly in the male group. Several of these genes, including *ATP5B*, *ATP5A1*, *MRPL23*, *AFG3L2*, and *ABCG2*, are related to energy metabolism. Four genes, including *BEX1*, *UBL4A*, *CD99*, and *MID1*, were located on sex chromosome [13]. By using a large European-wide sample in their meta-analysis, Perez-Becerril et al. [66] found the risk alleles of two *SLC30A3* variants in females, which were associated with gene expression. In a meta-analysis of 41 studies, it has been shown a significant increase in expression of pro-inflammatory genes, including *IL-1 β* , *IL-6*, and *TNF- α* on transcript and protein levels in patients with SCZ [79].

2.5.2. Micro-ribonucleic acids (miRNAs) studies

These RNAs are small noncoding RNA molecules which exert their functions by pairing with messenger RNAs (mRNAs) [80] and are powerful negative regulators of gene expression [81, 82]. They function in cell proliferation and death, patterning of the nervous system, and also as modulators of target mRNA translation and stability [83], RNA silencing and post-transcriptional regulation of gene expression [84]. There are different sets of miRNAs expressed in different cell types and tissues [85] and in many other biological processes, such as insulin secretion, B-cell development [86], hematopoiesis [87], and metabolic biochemistry [81]. Aberrant miRNA expression is implicated in many disorders, such as cancers [88], ischemic heart diseases [82], and mental disorders as well. A huge amount of evidence implicates miRNAs as a class of modulator for human tumor initiation and progression [80]. However, miRNA-based therapies are under investigation. In a meta-analysis, Ma et al. [9] reported that *miR-137* genetic variant rs1625579 is significantly associated with SCZ. Additionally, in another meta-analysis of 52 GWASs completed in 2014, Hauberg et al. [10] showed that the SCZ risk genes were regulated by miRNAs ($P < 2 \times 10^{-16}$). The strongest miRNAs were *miR-9-5p*, *miR485-5p*, and *miR-137* [9].

2.5.3. Transcriptome and proteome studies

Transcriptome is the set of all RNA molecules (transcripts) in one cell, a population of cells or in a given organism. The study of transcriptome examines the expression level of RNAs in a given cell population, often focusing on mRNA, but sometimes including others such as transfer RNAs (tRNAs) and soluble RNAs (sRNAs).

The proteome is the entire set of proteins expressed by a genome in a cell, tissue, or organism at a certain time, under defined conditions. Proteomics is the study of the proteome. Understanding of the implication of genetic variations in mental disorders requires translation into functional effects [70]. New technologies allow the investigation of levels of mRNAs and proteins at the same time [89].

A significant increased expression of *SLC2A3*—glucose transporter, and *DAAM2*—actin assembly factor, and a significant decreased expression of *OMA1*—zinc metallopeptidase,

NLN1, and *MYBPC3*—myosin C have been reported in the first onset of SCZ [90]. The peripheral mRNA of these genes may be potential biomarkers in early stages of disorder course [89].

3. Epigenetics of schizophrenia

3.1. Epigenetics and epigenetics code

The Greek prefix *epi-* (“over”) in epigenetics implies features that are “on top of” or “in addition to” the traditional genetic basis for inheritance (**Table 1**). Epigenetics is the study of changes in gene functions, including gene expression that are heritable and that does not entail a change in DNA sequence [91]. Examples of epigenetic mechanisms are DNA methylation and acetylation and also histone modifications. The epigenetic changes are potentially reversible. Epigenetic codes are heritable DNA/histone modifications that specify patterns of gene expression through differentiation and development [92].

3.2. Epigenetic study of schizophrenia

Epigenotyping might be integrated along with genotyping and phenotyping as means of implementing advanced precision medicine [93]. Epigenetic mechanisms regulate the key neurobiological and cognitive processes in the brain [94]. Epigenetic drugs, such as histone de-acetylation, and DNA methylation inhibitors have received increased attention for the management of mental disorders [95].

Neuroepigenomics represents an effort to unify the research available on the molecular pathology of mental disorders, such as single DNA methylation, to epigenome-wide association studies, post-translational modifications of histones, or nucleosomal positioning [96]. A huge amount of studies examining the role of epigenome, including epigenetic signaling, such as DNA and histone modifications in the etiology of SCZ was published [97, 98]. Large-scale consortia, such as the PGC and the Common Minds Consortium provide detailed insight into the epigenetic risk architectures of SCZ [99]. However, the absence of consistently replicated genetic effects together with changes in gene expression suggests the role of epigenetic mechanisms in SCZ [16].

Brain development is guided by interactions between the genome and environment, such as early life adversity. Epigenetic mechanisms can mediate these interactions and increase the risk of SCZ [17]. In a mixed model of SCZ risk, abnormal epigenetic states with large effects are superimposed on a polygenic liability to SCZ [100]. It has been reported that several genes related to nucleosome and histone structure are dysregulated in PBMC of patients with SCZ. It may be suggesting a potential epigenetic mechanism underlying the risk factor for the development of SCZ [101].

Genome-scale mapping of epigenetic mechanisms, including chromosomal loopings, and other epigenetic determinants of genome organization help to understand the mechanisms contributing to dysregulated expression of synaptic and metabolic genes in SCZ [102]. Some authors have found methylation differences in different genes, including *COMT*, *RELN*, and in some other genes implicated in dopaminergic, serotonergic, γ -aminobutyric acid (GABA)ergic, and glutamatergic pathways [103]. It has been proposed that prenatal stress induces neurodevelopmental

alterations in the prefrontal cortex that are expressed as cognitive impairments observed in SCZ [104]. Reelin (*RELN*) is involved in cortical neural connectivity and synaptic plasticity. Downregulation of *RELN* expression due to its hypermethylation has been associated with epigenetic changes in this gene of the prefrontal cortex of patients with SCZ [97].

A significant portion of patients with SCZ shows deficits in glutamate decarboxylase 1 (*GAD1*). This gene encodes a 67 kDa glutamate decarboxylase (*GAD67*) protein in multiple areas of adult cerebral cortex. This event, possibly reflecting molecular defects in subtypes of GABAergic interneurons essential for network synchronization and cognition [105]. Dysfunction of prefrontal cortex in SCZ includes the changes in GABAergic mRNAs, including decreased expression of *GAD1*. It has been demonstrated that the methylation frequency at CpG dinucleotides located at the proximal *GAD1* promoter shows a significant deficit in repressive DNA methylation in patients with SCZ [106]. Adverse life events have been found to control DNA methylation in postmitotic neurons. This phenotype in SCZ was accompanied by a persistent increase in *AVP* gene expression [107].

4. Pathway analysis

4.1. An overview

The concept of pathway is more complex structure than a cluster. Pathways in biology correspond to series of interactions among different molecules in a cell that lead to a certain product. Pathway-based analysis provides a technique, which allows a comprehensive understanding of the molecular mechanisms underlying complex traits or disorders, such as mental disorders. There are a variety of pathway-based approaches, including SNP/GWAS-derived pathway analysis, which correspond to different research designs and data types [108].

In pathway analysis, data come from high throughput biology. Gene sets corresponding to biological pathways are tested for significant relationships with a phenotype. Genotyping, gene expression arrays, or any data elements that could be mapped to genes or gene products could be used. It may be concluded that the pathway analysis represents a potentially powerful and biologically-oriented bridge between genotypes and phenotypes [109]. Pathway analysis has become the first choice for gaining insight into the underlying biology of differentially expressed genes and proteins, as it reduces complexity and has increased explanatory power [110].

4.2. Pathway analysis in schizophrenia

By using the key words of “genome-wide association study” in PubMed database, over 22,000 human GWAS publications have described genetic associations to a wide range of disorders and traits. Additionally, by using the key words of “genome-wide association study and schizophrenia” in PubMed, more than 1190 human GWAS publications have described genetic associations to SCZ. Genome-wide data sets are increasingly viewed as foundations for discovering pathways and networks relevant to phenotypes [111]. However, extending GWAS findings to mechanistic hypotheses about the development of SCZ has been a major ongoing challenge.

Sundararajan et al. [22] have been used the clinically relevant and reported susceptibility genes associated with SCZ and available gene analysis program, and created a molecular profile of the updated SCZ genes. These genes were predominantly expressed in specific brain regions, including the cerebellum, cerebral cortex, medulla oblongata, thalamus, and hypothalamus. Interestingly, by the analysis of major biological pathways and mechanisms associated with SCZ genes, these authors identified glutaminergic, serotonergic, GABAergic, and dopaminergic receptors, calcium-related channels, solute transporters, and neurodevelopmental genes. Biological mechanisms, including synaptic transmission, membrane potential, and transmembrane ion transport regulation were identified as leading molecular functions associated with SCZ genes [22].

Regarding the involvement of neuroinflammation in pathogenesis of SCZ in postmortem brains of patients with SCZ, neuroinflammatory markers and an overall increase in expression of pro-inflammatory genes have been reported [79].

By using a translational convergent functional genomics approach and a poly evidence scoring and pathway analyses, Ayalew et al. [51] identified top genes (e.g., *DISC1*, *HSPA1B*, *MBP*, and *TCF4*), brain development, myelination, cell adhesion, glutamate receptor signaling, G-protein coupled receptor signaling, and cAMP-mediated signaling as key to pathophysiology and as targets for therapeutic intervention.

Karim et al. [76] carried out pathway and gene ontology analyses and observed alteration in a few signaling pathways in neurons. These pathways were GABA receptor, immune response, G beta gamma, dopamine and cyclic AMP, complement system, axonal guidance, dendritic cell maturation, *CREB*, and interleukin-1 signaling pathways and networks.

By using the network-based approach for evaluating gene co-expression, Mistry et al. [112] found separate gene co-expression networks. Functional enrichment analysis showed that altered genes expression in SCZ associate with biological processes such as oxidative phosphorylation, myelination, synaptic transmission, and immune function [112].

Differentially expressed genes in PBMC of patients with SCZ have been reported that were involved in pathways such as cell adhesion, neuronal guidance, neurotrophins, oxidative stress, glucose metabolism, apoptosis, and cell-cycle regulation [78].

It has been suggested that the genetic basis of SCZ has a complex evolutionary history. It has been hypothesized that the genetic architecture components of SCZ are attributable to human lineage-specific evolution [113]. It has been shown that the SCZ genes are located near previously identified human accelerated regions (HARs). Additionally, these genes enrich in a GABA-related co-expression module significantly. These genes are differentially regulated in patients with SCZ. It has been concluded that genes located near the HARs are associated with important functional roles in the genetic architecture of SCZ [113].

Cell death is an active process that maintains tissue homeostasis. Three types of distinct cell death are apoptosis, autophagic cell death, and necrosis [114]. The apoptotic pathway will begin with death receptor activation. This activation leads to the formation of death receptor signaling pathways, resulting in the demolition of the cell [115]. It has been hypothesized that

an increase in apoptosis may underlie neuropathology of SCZ [116]. There are significant expression changes in death genes receptor signaling pathways in the dorsolateral prefrontal cortex of patients with SCZ, including the *TNFSF13* and *TNFSF13*. It has been concluded that the increased *TNFSF13* expression may be one of the abnormalities that contribute to the brain pathology in SCZ [116].

By using the factor analysis of symptoms of narrowly defined patients with SCZ through the clinician-rated operational criteria checklist items in an Irish family sample, implemented genome-wide association, gene-based, and gene-pathway analyses of these SCZ-based symptom factors, Docherty et al. [117] could find three factors, including: a manic, a depressive, and a positive symptom factor. Gene-based analysis of these factors showed *PTPRG* and *WBP1L* genes. These genes were also implicated by the PGC study of SCZ [45]. It has been suggested that variants in these two genes might also act as modifiers of SCZ symptoms. Gene pathway analysis of the mania factor indicated over-representation of glutamatergic transmission, GABA-A receptor, and cyclic GMP pathways and these pathways may have differential influence on affective symptoms in SCZ [117].

Through the interrogating SCZ genes and their complex interactions at various levels, including transcripts and proteins and also environmental and developmental factors, our knowledge and insight into the disorder processes will increase. This may possibly open the new avenues for more effective therapeutic interventions.

5. Future perspective

Although a huge amount of studies has been performed and significant progress has been made in past decades, the high heritability, phenotype heterogeneity, and strong genetic and epigenetic heterogeneity of SCZ still post as major challenges to the genetic dissection of this complex syndrome. Therefore, more studies are needed to explain its missing heritability [118]. It is essential to shift paradigm in understanding the etiopathology of SCZ. A critical question is “What is schizophrenia?” Is it a specific disorder or a heterogeneous syndrome? Changes in brain gene expression of the patients with SCZ may reflect the possible pathways related to pathophysiology of the syndrome.

A few suggestions for the next decade are studying the multiple brain regions in normal people to better understand neural circuitry, genetics and epigenetic patterns of the brain, peripheral biomarker studies, and analyze the other omics data, such as transcriptomics across a developmental series of brains. System biology and computational approaches will be useful to advance from normal brains to a more reliable and valid definition of the SCZ interactome and connectome [70].

Through the better understanding of pathophysiology of SCZ, at the levels of genetic and epigenetic, we could identify new leads for the management of this complex syndrome. However, which gene(s) is causal, how the risk genetic or epigenetic factors alter gene expression, and how they fit into pathology and syndrome pathways [119]. New drugs for SCZ are

essential needs for the patients. These drugs have to target pathophysiological alterations that are specific to syndrome. Schizophrenia is a multifactorial and strongly biologically heterogeneous syndrome. Identification of homogenous subgroups is increasingly necessary for new drugs discovery [120]. So, the above mentioned assays will help the researchers to understand the pathological processes and the development of better treatments [15, 119].

In addition to different approaches to the analysis for genes associated with SCZ, the genetics and epigenetic of specific psychopathology, including cognitive impairments, negative signs, disorganized behaviors, etc., need to be addressed. In this regard, neuroimaging genetics approach will be useful. In addition, a psychiatric translational and phenomics approach (genome to mind phenome), understanding the pathology of syndrome in different levels, such as genetics, epigenetic, proteomics, and other omics data, and also neural circuit abnormalities, and endophenotypes related to psychopathology and clinical phenotypes are another essential steps.

6. Conclusion

Schizophrenia is a complex, heterogeneous, and multifactorial syndrome. It has many levels, including genomics, epigenomics, transcriptomics, proteomics, metabolomics, neural circuit, endophenotype, and albeit clinical presentations. It seems that an ideal “multi-level diagnostic system” has to include all of these levels to make a bioprofile. By doing this in the near future, we hope to have a more reliable and valid diagnostic system, better approach to its treatment and also prevention of mental disorders, including SCZ.

Conflict of interest

The author declares to have no conflicts of interest.

Author details

Esmail Shamsavand Ananloo

Address all correspondence to: esmailshamsavand@gmail.com

Department of Genomic Psychiatry and Behavioral Genomics (DGPBG), Roozbeh Hospital, School of Medicine, Tehran University of Medical Sciences (TUMS), Tehran, Iran

References

- [1] Birnbaum R, Weinberger DR. Genetic insights into the neurodevelopmental origins of schizophrenia. *Nature Reviews. Neuroscience*. Dec 2017;18(12):727-740. DOI: 10.1038/nrn.2017.125

- [2] Vita A, Barlati S, De Peri L, et al. Schizophrenia. *Lancet*. 2016;**388**(10051):1280. DOI: 10.1016/S0140-6736(16)31674-9
- [3] Aberg KA, Liu Y, Bukszár J, et al. A comprehensive family-based replication study of schizophrenia genes. *JAMA Psychiatry*. Jun 2013;**70**(6):573-581. DOI: 10.1001/jamapsychiatry.2013.288
- [4] Pantavou KG, Braliou GG, Kontou PI, et al. A meta-analysis of FZD3 gene polymorphisms and their association with schizophrenia. *Psychiatric Genetics*. Dec 2016;**26**(6):272-280. DOI: 10.1097/YPG.0000000000000155
- [5] Gottesman II, Erlenmeyer-Kimling L. Family and twin strategies as a head start in defining prodromes and endophenotypes for hypothetical early-interventions in schizophrenia. *Schizophrenia Research*. Aug 1, 2001;**51**(1):93-102. DOI: 10.1016/s0920-9964(01)00245-6
- [6] Fatemi SH, Folsom TD, Rooney RJ, et al. The viral theory of schizophrenia revisited: Abnormal placental gene expression and structural changes with lack of evidence for H1N1 viral presence in placentae of infected mice or brains of exposed offspring. *Neuropharmacology*. Mar 2012;**62**(3):1290-1298. DOI: 10.1016/j.neuropharm.2011.01.011
- [7] Meyer U, Feldon J. Epidemiology-driven neurodevelopmental animal models of schizophrenia. *Progress in Neurobiology*. Mar 2010;**90**(3):285-326. DOI: 10.1016/j.pneurobio.2009.10.018
- [8] Niculescu AB. Schizophrenia: From genetics to biology to predictive medicine. *The Journal of Clinical Psychiatry*. 2014;**75**(Suppl 2):4-7. DOI: 10.4088/JCP.13065su1.01
- [9] Ma G, Yin J, Fu J, et al. Association of a miRNA-137 polymorphism with schizophrenia in a southern Chinese Han population. *BioMed Research International*. 2014;**2014**:751267. DOI: 10.1155/2014/751267
- [10] Hauberg ME, Roussos P, Grove J, Børglum AD, Mattheisen M, Schizophrenia Working Group of the Psychiatric Genomics Consortium. Analyzing the role of MicroRNAs in schizophrenia in the context of common genetic risk variants. *JAMA Psychiatry*. Apr 2016;**73**(4):369-377. DOI: 10.1001/jamapsychiatry.2015.3018
- [11] Liu W, Liu F, Xu X, Bai Y. Replicated association between the European GWAS locus rs10503253 at CSMD1 and schizophrenia in Asian population. *Neuroscience Letters*. Apr 2017;**24**(647):122-128. DOI: 10.1016/j.neulet.2017.03.039
- [12] Mostaid MS, Mancuso SG, Liu C, et al. Meta-analysis reveals associations between genetic variation in the 5' and 3' regions of Neuregulin-1 and schizophrenia. *Translational Psychiatry*. Jan 17, 2017;**7**(1):e1004. DOI: 10.1038/tp.2016.279
- [13] Qin W, Liu C, Sodhi M, Lu H. Meta-analysis of sex differences in gene expression in schizophrenia. *BMC Systems Biology*. Jan 11, 2016;**10**(Suppl 1):9. DOI: 10.1186/s12918-015-0250-3
- [14] Alizadeh F, Tavakkoly-Bazzaz J, Bozorgmehr A, Azarnezhad A, Tabrizi M, Shahsavand AE. Association of transcription factor 4 (TCF4) gene mRNA level with schizophrenia,

- its psychopathology, intelligence and cognitive impairments. *Journal of Neurogenetics*. Dec 2017;**31**(4):344-351. DOI: 10.1080/01677063.2017.1396330
- [15] Hoffmann A, Ziller M, Spengler D. The future is the past: Methylation QTLs in schizophrenia. *Genes (Basel)*. Nov 24, 2016;**7**(12). DOI: 10.3390/genes7120104
- [16] Cariaga-Martinez A, Saiz-Ruiz J, Alelú-Paz R. From linkage studies to epigenetics: What we know and what we need to know in the neurobiology of schizophrenia. *Frontiers in Neuroscience*. May 11, 2016;**10**:202. DOI: 10.3389/fnins.2016.00202
- [17] Hoffmann A, Sportelli V, Ziller M, Spengler D. Epigenomics of major depressive disorders and schizophrenia: Early life decides. *International Journal of Molecular Sciences*. Aug 4, 2017;**18**(8):pii:E1711. DOI: 10.3390/ijms18081711
- [18] Fisch GS. Whither the genotype-phenotype relationship? An historical and methodological appraisal. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*. Sep 2017;**175**(3):343-353. DOI: 10.1002/ajmg.c.31571
- [19] Owens EM, Bachman P, Glahn DC, Bearden CE. Electrophysiological Endophenotypes for schizophrenia. *Harvard Review of Psychiatry*. Mar–Apr 2016;**24**(2):129-147. DOI: 10.1097/HRP.0000000000000110
- [20] DiLalla LF, McCrary M, Diaz E. A review of endophenotypes in schizophrenia and autism: The next phase for understanding genetic etiologies. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics*. Sep 2017;**175**(3):354-361. DOI: 10.1002/ajmg.c.31566
- [21] Reble E, Castellani CA, Melka MG, et al. VarScan2 analysis of de novo variants in monozygotic twins discordant for schizophrenia. *Psychiatric Genetics*. Apr 2017;**27**(2):62-70. DOI: 10.1097/YPG.0000000000000162
- [22] Sundararajan T, Manzardo AM, Butler MG. Functional analysis of schizophrenia genes using GeneAnalytics program and integrated databases. *Gene*. Jan 30, 2018;**(641)**:25-34. DOI: 10.1016/j.gene.2017.10.035
- [23] Tansey KE, Owen MJ, O'Donovan MC. Schizophrenia genetics: Building the foundations of the future. *Schizophrenia Bulletin*. Jan 2015;**41**(1):15-19. DOI: 10.1093/schbul/sbu162
- [24] Kotlar AV, Mercer KB, Zwick ME, Mulle JG. New discoveries in schizophrenia genetics reveal neurobiological pathways: A review of recent findings. *European Journal of Medical Genetics*. Dec 2015;**58**(12):704-714. DOI: 10.1016/j.ejmg.2015.10.008
- [25] Wray NR, Goddard ME, Visscher PM. Prediction of individual genetic risk to disease from genome-wide association studies. *Genome Research*. Oct 2007;**17**(10):1520-1528. DOI: 10.1101/gr.6665407
- [26] Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: Evidence from a meta-analysis of twin studies. *Archives of General Psychiatry*. 2003;**60**(12):1187-1192. DOI: 10.1001/archpsyc.60.12.1187

- [27] Cardno AG, Gottesman II. Twin studies of schizophrenia: From bow-and-arrow concordances to star wars mx and functional genomics. *American Journal of Medical Genetics*. 2000 Spring;**97**(1):12-17. DOI: 10.1002/(SICI)1096-8628(200021)97:1<12::AID-AJMG3>3.0.CO;2-U
- [28] Lichtenstein P, Yip BH, Björk C, et al. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: A population-based study. *Lancet*. Jan 17, 2009;**373**(9659):234-239. DOI: 10.1016/S0140-6736(09)60072-6
- [29] Scolnick EM. The path to new therapies for schizophrenia and bipolar illness. *The FASEB Journal*. Apr 2017;**31**(4):1254-1259. DOI: 10.1096/fj.201700028
- [30] Janoutová J, Janácková P, Serý O, et al. Epidemiology and risk factors of schizophrenia. *Neuro Endocrinology Letters*. 2016;**37**(1):1-8. DOI: 10.1007/s11469-009-9241-1
- [31] Roalf DR, Vandekar SN, Almasy L, et al. Heritability of subcortical and limbic brain volume and shape in multiplex-multigenerational families with schizophrenia. *Biological Psychiatry*. Jan 15, 2015;**77**(2):137-146. DOI: 10.1016/j.biopsych.2014.05.009
- [32] Voineskos AN. Genetic underpinnings of white matter 'connectivity': Heritability, risk, and heterogeneity in schizophrenia. *Schizophrenia Research*. Jan 2015;**161**(1):50-60. DOI: 10.1016/j.schres.2014.03.034
- [33] Mark W, Touloupoulou T. Cognitive intermediate phenotype and genetic risk for psychosis. *Current Opinion in Neurobiology*. Feb 2016;**36**:23-30. DOI: 10.1016/j.conb.2015.08.008
- [34] Plomin R, Haworth CM, Meaburn EL, et al. Common DNA markers can account for more than half of the genetic influence on cognitive abilities. *Psychological Science*. Apr 2013;**24**(4):562-568. DOI: 10.1177/0956797612457952
- [35] Farrell MS, Werge P, Sklar MJ, et al. Evaluating historical candidate genes for schizophrenia. *Molecular Psychiatry*. 2015;**20**(5):555-562. DOI: 10.1038/mp.2015.16
- [36] Patnala R, Clements J, Batra J. Candidate gene association studies: A comprehensive guide to useful in silico tools. *BMC Genetics*. May 9, 2013;**14**:39. DOI: 10.1186/1471-2156-14-39
- [37] Kwon JM, Goate AM. The candidate gene approach. *Alcohol Research & Health*. 2000;**24**(3):164-168
- [38] Lee S, Wright FA, Zou F. Control of population stratification by correlation-selected principal components. *Biometrics*. 2011;**67**:967-974. DOI: 10.1111/j.1541-0420.2010.01520.x
- [39] Burdick KE, DeRosse P, Kane JM, et al. Genetic variation in the MET proto-oncogene is associated with schizophrenia and general cognitive ability. *The American Journal of Psychiatry*. 2010;**167**(4):436-443. DOI: 10.1176/appi.ajp.2009.09050615
- [40] Lander ES, Linton LM, Birren B, et al. Initial sequencing and analysis of the human genome. *Nature*. 2001;**409**(6822):860-921. DOI: 10.1038/35057062
- [41] International HapMap Consortium. A haplotype map of the human genome. *Nature*. 2005;**437**(7063):1299-1320. DOI: 10.1038/nature04226

- [42] The 1000 Genomes Project Consortium, Abecasis GR, Auton A, et al. An integrated map of genetic variation from 1,092 human genomes. *Nature*. 2012;**491**:56-65. DOI: 10.1038/nature11632
- [43] Pritchard JK, Cox NJ. The allelic architecture of human disease genes: common disease-common variant or not? *Human Molecular Genetics*. 2002;**11**:2417-2423. DOI: 10.1093/hmg/11.20.2417
- [44] Stefansson H, Ophoff RA, Steinberg S, et al. Common variants conferring risk of schizophrenia. *Nature*. 2009;**460**:744-747. DOI: 10.1038/nature08186
- [45] Ripke S, Sanders AR, Kendler KS, et al. Genome-wide association study identifies five new schizophrenia loci. *Nature Genetics*. 2011;**43**:969-976. DOI: 10.1038/ng.940
- [46] Mccarroll SA, Altshuler DM. Copy number variation and association studies of human diseased. *Nature Genetics*. 2007;**39**:37-42. DOI: 10.1038/ng2080
- [47] Bassett AS, Scherer SW, Brzustowicz LM. Copy number variations in schizophrenia: Critical review and new perspectives on concepts of genetics and disease. *The American Journal of Psychiatry*. 2010;**167**:899-914. DOI: 10.1176/appi.ajp.2009.09071016
- [48] Xu B, Roos JL, Levy S, et al. Strong association of de novo copy number mutations with sporadic schizophrenia. *Nature Genetics*. Jul, 2008;**40**(7):880-885. DOI: 10.1038/ng.162
- [49] Vacic V, McCarthy S, Malhotra D, et al. Duplications of the neuropeptide receptor gene VIPR2 confer significant risk for schizophrenia. *Nature*. 2011;**471**:499-503. DOI: 10.1038/nature09884
- [50] Allen NC, Bagade S, McQueen MB, et al. Systematic meta-analyses and field synopsis of genetic association studies in schizophrenia: The SzGene database. *Nature Genetics*. 2008;**40**(7):827-834. DOI: 10.1038/ng.171
- [51] Ayalew M, Le-Niculescu H, Levey DF, et al. Convergent functional genomics of schizophrenia: From comprehensive understanding to genetic risk prediction. *Molecular Psychiatry*. 2012;Sep;**17**(9):887-905. DOI: 10.1038/mp.2012.37
- [52] Kheirollahi M, Kazemi E, Ashouri S. Brain-derived Neurotrophic factor gene Val66Met polymorphism and risk of schizophrenia: A meta-analysis of case-control studies. *Cellular and Molecular Neurobiology*. Jan 2016;**36**(1):1-10. DOI: 10.1007/s10571-015-0229-z
- [53] González-Castro TB, Hernández-Díaz Y, Juárez-Rojop IE, et al. The role of C957T, TaqI and Ser311Cys polymorphisms of the DRD2 gene in schizophrenia: Systematic review and meta-analysis. *Behavioral and Brain Functions*. Nov 9, 2016;**12**(1):29. DOI: 10.1186/s12993-016-0114-z
- [54] Neale BM, Sham PC. The future of association studies: Gene-based analysis and replication. *American Journal of Human Genetics*. 2004;**75**(3):353-362. DOI: 10.1086/423901
- [55] Sullivan PF. Spurious genetic associations. *Biological Psychiatry*. 2007;**61**(10):1121-1126. DOI: 10.1016/j.biopsych.2006.11.010

- [56] Agrawal A, Edenberg HJ, Gelernter J. Meta-analyses of genome-wide association data hold new promise for addiction genetics. *Journal of Studies on Alcohol and Drugs*. 2016 Sep;**77**(5):676-680. DOI: 10.15288/jsad.2016.77.676
- [57] Lencz T, Knowles E, Davies G, et al. Molecular genetic evidence for overlap between general cognitive ability and risk for schizophrenia: a report from the Cognitive Genomics consorTium (COGENT). *Molecular Psychiatry*. Feb 2014;**19**(2):168-174. DOI: 10.1038/mp.2013
- [58] Luo XJ, Huang L, Oord EJ, et al. Common variants in the MKL1 gene confer risk of schizophrenia. *Schizophrenia Bulletin*. May 2015;**41**(3):715-727. DOI: 10.1093/schbul/sbu156
- [59] Sleiman P, Wang D, Glessner J, et al. GWAS meta analysis identifies TSNARE1 as a novel schizophrenia/bipolar susceptibility locus. *Scientific Reports*. Oct 29, 2013;**3**:3075. DOI: 10.1038/srep03075
- [60] Xu C, Aragam N, Li X, et al. BCL9 and C9orf5 are associated with negative symptoms in schizophrenia: Meta-analysis of two genome-wide association studies. *PLoS One*. 2013;**8**(1):e51674. DOI: 10.1371/journal.pone.0051674
- [61] Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*. 2014;**511**:421-427. DOI: 10.1038/nature13595
- [62] Rose EJ, Morris DW, Hargreaves A, et al. Neural effects of the CSMD1 genome-wide associated schizophrenia risk variant rs10503253. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*. Sep 2013;**162B**(6):530-537. DOI: 10.1002/ajmg.b.32182
- [63] Koiliari E, Roussos P, Pasparakis E, et al. The CSMD1 genome-wide associated schizophrenia risk variant rs10503253 affects general cognitive ability and executive function in healthy males. *Schizophrenia Research*. Apr 2014;**154**(1-3):42-47. DOI: 10.1016/j.schres.2014.02.017
- [64] Suárez-Rama JJ, Arrojo M, Sobrino B, et al. Resequencing and association analysis of coding regions at twenty candidate genes suggest a role for rare risk variation at AKAP9 and protective variation at NRXN1 in schizophrenia susceptibility. *Journal of Psychiatric Research*. Jul-Aug, 2015;**66-67**:38-44. DOI: 10.1016/j.jpsychires.2015.04.013
- [65] Takahashi S, Glatt SJ, Uchiyama M, et al. Meta-analysis of data from the psychiatric genomics consortium and additional samples supports association of CACNA1C with risk for schizophrenia. *Schizophrenia Research*. Oct, 2015;**168**(1-2):429-433. DOI: 10.1016/j.schres.2015.07.033
- [66] Perez-Becerril C, Morris AG, Mortimer A, et al. Common variants in the chromosome 2p23 region containing the SLC30A3 (ZnT3) gene are associated with schizophrenia in female but not male individuals in a large collection of European samples. *Psychiatry Research*. Dec 30, 2016;**246**:335-340. DOI: 10.1016/j.psychres.2016.09.052

- [67] Chang H, Zhang C, Xiao X, et al. Further evidence of VRK2 rs2312147 associated with schizophrenia. *The World Journal of Biological Psychiatry*. Sep 2016;**17**(6):457-466. DOI: 10.1080/15622975.2016.1200746
- [68] Xiao X, Li M. Replication of Han Chinese GWAS loci for schizophrenia via meta-analysis of four independent samples. *Schizophrenia Research*. Apr 2016;**172**(1-3):75-77. DOI: 10.1016/j.schres.2016.02.019
- [69] DeLisi LE. Is schizophrenia a lifetime disorder of brain plasticity, growth and aging? *Schizophrenia Research*. Feb 7, 1997;**23**(2):119-129. DOI: 10.1016/S0920-9964(96)00079-5
- [70] Sequeira PA, Martin MV, Vawter MP. The first decade and beyond of transcriptional profiling in schizophrenia. *Neurobiology of Disease*. Jan 2012;**45**(1):23-36. DOI: 10.1016/j.nbd.2011.03.001
- [71] Palaniyappan L. Progressive cortical reorganisation: A framework for investigating structural changes in schizophrenia. *Neuroscience and Biobehavioral Reviews*. Aug 2017;**79**:1-13. DOI: 10.1016/j.neubiorev.2017.04.028
- [72] Dietsche B, Kircher T, Falkenberg I. Structural brain changes in schizophrenia at different stages of the illness: A selective review of longitudinal magnetic resonance imaging studies. *The Australian and New Zealand Journal of Psychiatry*. May 2017;**51**(5):500-508. DOI: 10.1177/0004867417699473
- [73] Heilbronner U, Samara M, Leucht S, et al. The longitudinal course of schizophrenia across the lifespan: Clinical, cognitive, and neurobiological aspects. *Harvard Review of Psychiatry*. Mar-Apr 2016;**24**(2):118-128. DOI: 10.1097/HRP.0000000000000092
- [74] van Os J, Rutten BP, Poulton R. Gene-environment interactions in schizophrenia: Review of epidemiological findings and future directions. *Schizophrenia Bulletin*. Nov 2008;**34**(6):1066-1082. DOI: 10.1093/schbul/sbn117
- [75] Popov NT, Stoyanova VK, Madzhirova NP, Vachev TI. Epigenetic aspects in schizophrenia etiology and pathogenesis. *Folia Medica (Plovdiv)*. Apr-Jun 2012;**54**(2):12-16. DOI: 10.2478/v10153-011-0082-x
- [76] Karim S, Kamal MA, Iqbal Z, et al. Global expression studies of schizophrenic brain: A meta-analysis study linking neurological immune system with psychological disorders. *CNS & Neurological Disorders Drug Targets*. 2016;**15**(4):477-488. DOI: 10.2174/1871527315666160321105216
- [77] Gardiner EJ, Cairns MJ, Liu B, et al. Gene expression analysis reveals schizophrenia-associated dysregulation of immune pathways in peripheral blood mononuclear cells. *Journal of Psychiatric Research*. Apr 2013;**47**(4):425-437. DOI: 10.1016/j.jpsychires.2012.11.007
- [78] van Beveren NJ, Buitendijk GH, Swagemakers S, et al. Marked reduction of AKT1 expression and deregulation of AKT1-associated pathways in peripheral blood mononuclear cells of schizophrenia patients. *PLoS One*. 2012;**7**:e32618. DOI: 10.1371/journal.pone.0032618

- [79] van Kesteren CF, Gremmels H, de Witte LD, et al. Immune involvement in the pathogenesis of schizophrenia: A meta-analysis on postmortem brain studies. *Translational Psychiatry*. Mar 28, 2017;**7**(3):e1075. DOI: 10.1038/tp.2017.4
- [80] Li C, Feng Y, Coukos G, Zhang L. Therapeutic MicroRNA strategies in human cancer. *The AAPS Journal*. Dec 2009;**11**(4):747. DOI: 10.1208/s12248-009-9145-9
- [81] Wilfred BR, Wang WX, Nelson PT. Energizing miRNA research: A review of the role of miRNAs in lipid metabolism, with a prediction that miR-103/107 regulates human metabolic pathways. *Molecular Genetics and Metabolism*. Jul 2007;**91**(3):209-217. DOI: 10.1016/j.ymgme.2007.03.011
- [82] Fasanaro P, Greco S, Ivan M, et al. microRNA: Emerging therapeutic targets in acute ischemic diseases. *Pharmacology & Therapeutics*. Jan 2010;**125**(1):92-104. DOI: 10.1016/j.pharmthera.2009.10.003
- [83] Lagos-Quintana M, Rauhut R, Yalcin A, et al. Identification of tissue-specific microRNAs from mouse. *Curr Biology*. Apr 30, 2002;**12**(9):735-739. DOI: 10.1016/S0960-9822(02)00809-6
- [84] Bartel DP. MicroRNAs: Genomics, biogenesis, mechanism, and function. *Cell*. Jan 23, 2004;**116**(2):281-297. DOI: 10.1016/S0092-8674(04)00045-5
- [85] Wienholds E, Kloosterman WP, Miska E, et al. MicroRNA expression in zebrafish embryonic development. *Science*. Jul 8, 2005;**309**(5732):310-311. DOI: 10.1126/science.1114519
- [86] Cuellar TL, McManus MT. MicroRNAs and endocrine biology. *The Journal of Endocrinology*. Dec 2005;**187**(3):327-332. DOI: 10.1677/joe.1.06426
- [87] Chen CZ, Li L, Lodish HF, Bartel DP. MicroRNAs modulate hematopoietic lineage differentiation. *Science*. Jan 2, 2004;**303**(5654):83-86. DOI: 10.1126/science.1091903
- [88] Trang P, Weidhaas JB, Slack FJ. MicroRNAs as potential cancer therapeutics. *Oncogene*. Dec 2008;**27**(Suppl 2):S52-S57. DOI: 10.1038/onc.2009.353
- [89] Lai CY, Scarr E, Udawela M, et al. Biomarkers in schizophrenia: A focus on blood based diagnostics and theranostics. *World Journal of Psychiatry*. Mar 22, 2016;**6**(1):102-117. DOI: 10.5498/wjp.v6.i1.102
- [90] Kuzman MR, Medved V, Terzic J, Krainc D. Genome-wide expression analysis of peripheral blood identifies candidate biomarkers for schizophrenia. *Journal of Psychiatric Research*. 2009;**43**:1073-1077. DOI: 10.1016/j.jpsychires.2009.03.005
- [91] Dupont C, Armant DR, Brenner CA. Epigenetics: Definition, mechanisms and clinical perspective. *Seminars in Reproductive Medicine*. Sep 2009;**27**(5):351-357. DOI: 10.1055/s-0029-1237423
- [92] Turner B. Defining an epigenetic code. *Nature Cell Biology*. 2007;**9**(1):2-6. DOI: 10.1038/ncb0107-2
- [93] Sweatt JD, Tamminga CA. An epigenomics approach to individual differences and its translation to neuropsychiatric conditions. *Dialogues in Clinical Neuroscience*. Sep 2016;**18**(3):289-298

- [94] Dempster E, Viana J, Pidsley R, Mill J. Epigenetic studies of schizophrenia: Progress, predicaments, and promises for the future. *Schizophrenia Bulletin*. Jan 2013;**39**(1):11-16. DOI: 10.1093/schbul/sbs139
- [95] Karsli-Ceppioglu S. Epigenetic mechanisms in psychiatric diseases and epigenetic therapy. *Drug Development Research*. Nov 2016;**77**(7):407-413. DOI: 10.1002/ddr.21340
- [96] Cariaga-Martinez A, Alelú-Paz R. Rethinking the epigenetic framework to unravel the molecular pathology of schizophrenia. *International Journal of Molecular Sciences*. Apr 7, 2017;**18**(4):pii:E790. DOI: 10.3390/ijms18040790
- [97] Ibi D, González-Maeso J. Epigenetic signaling in schizophrenia. *Cellular Signalling*. Oct 2015;**27**(10):2131-2136. DOI: 10.1016/j.cellsig.2015.06.003
- [98] Fullard JF, Halene TB, Giambartolomei C, et al. Understanding the genetic liability to schizophrenia through the neuroepigenome. *Schizophrenia Research*. Nov 2016;**177**(1-3): 115-124. DOI: 10.1016/j.schres.2016.01.039
- [99] Javidfar B, Park R, Kassim BS, et al. The epigenomics of schizophrenia, in the mouse. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*. Sep 2017;**174**(6): 631-640. DOI: 10.1002/ajmg.b.32566
- [100] Svrakic DM, Zorumski CF, Svrakic NM, et al. Risk architecture of schizophrenia: The role of epigenetics. *Current Opinion in Psychiatry*. Mar 2013;**26**(2):188-195. DOI: 10.1097/YCO.0b013e32835d8329
- [101] Glatt SJ, Stone WS, Nossova N, et al. Similarities and differences in peripheral blood gene-expression signatures of individuals with schizophrenia and their first-degree biological relatives. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*. 2011;**156B**:869-887. DOI: 10.1002/ajmg.b.31239
- [102] Akbarian S. Epigenetic mechanisms in schizophrenia. *Dialogues in Clinical Neuroscience*. Sep 2014;**16**(3):405-417
- [103] Rivollier F, Lotersztajn L, Chaumette B, et al. Epigenetics of schizophrenia: A review. *Encephale*. Oct 2014;**40**(5):380-386. DOI: 10.1016/j.encep.2014.06.005
- [104] Negrón-Oyarzo I, Lara-Vásquez A, Palacios-García I, et al. Schizophrenia and reelin: A model based on prenatal stress to study epigenetics, brain development and behavior. *Biological Research*. Mar 11, 2016;**49**:16. DOI: 10.1186/s40659-016-0076-5
- [105] Mitchell AC, Jiang Y, Peter C, Akbarian S. Transcriptional regulation of GAD1 GABA synthesis gene in the prefrontal cortex of subjects with schizophrenia. *Schizophrenia Research*. Sep 2015;**167**(1-3):28-34. DOI: 10.1016/j.schres.2014.10.020
- [106] Huang HS, Akbarian S. GAD1 mRNA expression and DNA methylation in prefrontal cortex of subjects with schizophrenia. *PLoS One*. Aug 29, 2007;**2**(8):e809. DOI: 10.1371/journal.pone.0000809
- [107] Murgatroyd C, Patchev AV, Wu Y, et al. Dynamic DNA methylation programs persistent adverse effects of early-life stress. *Nature Neuroscience*. Dec 2009;**12**(12):1559-1566. DOI: 10.1038/nn.2436

- [108] Jin LV, Zuo ZY, Su WY, et al. Pathway-based analysis tools for complex diseases. *Genomics, Proteomics & Bioinformatics*. Oct 2014;**12**(5):210-220. DOI: 10.1016/j.gpb.2014.10.002
- [109] Ramanan VK, Shen L, Moore JH, Saykin AJ. Pathway analysis of genomic data: Concepts, methods, and prospects for future development. *Trends in Genetics*. Jul 2012;**28**(7):323-332. DOI: 10.1016/j.tig.2012.03.004
- [110] Khatri P, Sirota M, Butte AJ. Ten years of pathway analysis: Current approaches and outstanding challenges. *PLoS Computational Biology*. 2012;**8**(2):e1002375. DOI: 10.1371/journal.pcbi.1002375
- [111] Hirschhorn JN. Genomewide association studies--illuminating biologic pathways. *The New England Journal of Medicine*. Apr 23, 2009;**360**(17):1699-1701. DOI: 10.1056/NEJMp0808934
- [112] Mistry M, Gillis J, Pavlidis P. Meta-analysis of gene coexpression networks in the post-mortem prefrontal cortex of patients with schizophrenia and unaffected controls. *BMC Neuroscience*. Sep 26, 2013;**14**:105. DOI: 10.1186/1471-2202-14-105
- [113] Xu K, Schadt EE, Pollard KS, et al. Genomic and network patterns of schizophrenia genetic variation in human evolutionary accelerated regions. *Molecular Biology and Evolution*. May 2015;**32**(5):1148-1160. DOI: 10.1093/molbev/msv031
- [114] Green DR, Llambi F. Cell death signaling. *Cold Spring Harbor Perspectives in Biology*. Dec 1, 2015;**7**(12). DOI: 10.1101/cshperspect.a006080
- [115] Lavrik IN. Systems biology of death receptor networks: Live and let die. *Cell Death & Disease*. May 29, 2014;**5**:e1259. DOI: 10.1038/cddis.2014.160
- [116] Catts VS, Weickert CS. Gene expression analysis implicates a death receptor pathway in schizophrenia pathology. *PLoS One*. 2012;**7**(4):e35511. DOI: 10.1371/journal.pone.0035511
- [117] Docherty AR, Bigdeli TB, Edwards AC, et al. Genome-wide gene pathway analysis of psychotic illness symptom dimensions based on a new schizophrenia-specific model of the OPCRIT. *Schizophrenia Research*. May 2015;**164**(1-3):181-186. DOI: 10.1016/j.schres.2015.02.013
- [118] Luo X, Huang L, Han L, et al. Systematic prioritization and integrative analysis of copy number variations in schizophrenia reveal key schizophrenia susceptibility genes. *Schizophrenia Bulletin*. Nov 2014;**40**(6):1285-1299. DOI: 10.1093/schbul/sbu045
- [119] Collier DA, Eastwood BJ, Malki K, Mokrab Y. Advances in the genetics of schizophrenia: Toward a network and pathway view for drug discovery. *Annals of the New York Academy of Sciences*. Feb 2016;**1366**(1):61-75. DOI: 10.1111/nyas.13066
- [120] Matsumoto M, Walton NM, Yamada H, et al. The impact of genetics on future drug discovery in schizophrenia. *Expert Opinion on Drug Discovery*. Jul 2017;**12**(7):673-686. DOI: 10.1080/17460441.2017.1324419

