World Journal of Psychiatry

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.5498/wjp.v3.i3.57

World J Psychiatr 2013 September 22; 3(3): 57-61
ISSN 2220-3206 (online)

EDITORIAL

New findings in the genetics of schizophrenia

Ladislav Hosak

Ladislav Hosak, Department of Clinical Studies, Faculty of Medicine, University of Ostrava, 708 33 Ostrava, Czech Republic
Ladislav Hosak, Department of Psychiatry, University Hospital Ostrava, 708 33 Ostrava, Czech Republic
Ladislav Hosak, Department of Psychiatry, School of Medicine, Charles University in Prague, 500 05 Hradec Kralove, Czech Republic
Ladislav Hosak, Department of Psychiatry, University Hospital Hradec Kralove, 500 05 Hradec Kralove,Czech Republic
Author contributions: Hosak L solely contributed to this paper.
Supported by The Research Grant NT14504/2013 from the Internal Grant Agency of the Ministry of Health of the Czech Republic
Correspondence to: Ladislav Hosak, MD, PhD, Professor of Psychiatry, Department of Psychiatry, University Hospital Hradec Kralove, Sokolska 581, 500 05 Hradec Kralove, Czech Republic. hosak@lfhk.cuni.cz
Telephone: +420-49-5832228 Fax: +420-49-5833041
Received: April 5, 2013 Revised: June 5, 2013
Accepted: July 18, 2013
Published online: September 22, 2013

Abstract

New findings in schizophrenia genetics are based on genome-wide association studies (GWAS), research into DNA copy number variations (CNVs), and endophenotypes. More than 70 genes have recently been suspected to be involved in the genetic background of schizophrenia based on the GWAS´s results. They are typically related to neurodevelopment/neuroplasticity, immunology and neuroendocrinology. Nevertheless, for many detected genes their possible relationship to schizophrenia etiopathogenesis is still unknown. The CNVs at genome loci 1q21.1 (candidate gene *e.g.*, *PRKAB2*), 2p16.3 (candidate gene *e.g.*, *NRXN1*), 3q29 (candidate genes *e.g.*, *BDH1*, *DLG1*, *PAK2* or *TFRC*), 15q11.2 (candidate gene *e.g.*, *CYFIP1*), 15q13.3 (candidate gene *e.g.*, *CHRNA7*), 16p13.1 (candidate genes *e.g.*,*NTAN1* or *NDE1*) and 22q11.2 (candidate genes *e.g.*, *COMT*, *GSTT2* or *PRODH*) were associated with schizophrenia most frequently. Genetic research of schizophrenia endophenotypes, usually neurophysiological, neuromotoric, neurocognitive, neuroanatomical, neurological or personality-related, will help us to discover the role of relevant genes in the pathogenesis of schizophrenia. It is also necessary to integrate knowledge from other research platforms in schizophrenia, like epigenetics, studies of gene-environment interactions, transcriptomics, proteomics, metabolomics, neuroimaging and psychopathology. A better knowledge of the genetic background of schizophrenia can lead to changes in the treatment, prevention and genetic counselling. It may also reduce stigma in this severe mental disorder.

Key words: Schizophrenia; Genetics; Genome-wide association study; Copy number variations; Endophenotypes

Core tip: New findings in schizophrenia genetics are based on genome-wide association studies (GWAS), research into DNA copy number variations (CNVs), and endophenotypes. More than 70 genes have been recently suspected to be involved in the genetic background of schizophrenia based on the GWAS´s results. The CNVs at genome loci 1q21.1, 2p16.3, 3q29, 15q11.2, 15q13.3, 16p13.1 and 22q11.2 were associated with schizophrenia most frequently. Genetic research of schizophrenia endophenotypes helps us to discover the role of relevant genes in the pathogenesis of schizophrenia. A better knowledge of the genetic background of schizophrenia can lead to changes in the treatment, prevention and genetic counselling.

Hosak L. New findings in the genetics of schizophrenia. *World J Psychiatr* 2013; 3(3): 57-61 Available from: URL: http://www.wjgnet.com/2220-3206/full/v3/i3/57.htm DOI: http://dx.doi.org/10.5498/wjp.v3.i3.57

INTRODUCTION

Schizophrenia (SZ) is a chronic disabling disease of the

brain. SZ affects 0.5%-1% 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. The causes of SZ consist of genetic and environmental factors[1]. Heritability of schizophrenia is mentioned to be up to 80%[2]. Even although we already have certain empirical data about the genetic basis of schizophrenia that implicate specific DNA loci, our recent knowledge on the genetics of schizophrenia is still nascent[3].

Genome-wide association studies, studies on DNA microdeletions/microduplications (genomic copy number variations), and genetic studies on schizophrenia endophenotypes represent three attitudes recently applied in the genetic research of schizophrenia.

GENOME-WIDE ASSOCIATION STUDIES

A genome-wide association study (GWAS), also known as a whole genome association study, is an examination of frequencies of single nucleotide polymorphisms (SNPs) in most of the genes of different individuals with or without a certain disease. The aim of the GWAS is to see how much the polymorphisms in genes vary among the affected (cases) compared to the unaffected subjects (controls)[4]. GWASs incorporate the power to detect small effects with the advantage of the positional genetics design, which requires no specific knowledge of pathogenesis. Published GWASs related to human diseases, including schizophrenia, are included in the National Human Genome Research Institute (NHGRI) GWAS Catalog[5]. The NHGRI is one of the 27 National Institutes of Health in the United States. GWAS is the most comprehensive procedure to discover a genetic background of complex diseases.

The NHGRI GWAS Catalog has recently covered 26 GWASs of schizophrenia. Their results have been summed up, *e.g.*, by Doherty *et al*[6] or Hosak *et al*[7]. More than 70 genes are suspected to be involved in the genetic background of schizophrenia based on the GWAS´s results. They are typically related to neurodevelopment/neuroplasticity (*e.g., AMBRA1*, *ANK3*, *DOCK4*, *LNX2*, *NRGN, NRG1*, *PRODH*, *RELN*, *SHISA9* or *TCF4*), immunology (*e.g., CSF2RA*, *HLA-DQA1*, *HLA-DRB1*, *IL3RA*, *PLAA*, *PRSS16*, *PTGS2*, *SPA17* or *TLR4*) and neuroendocrinology (*e.g., NRGN* or *PAM*). Nevertheless, for many detected genes (*e.g., ACSM1*, *AGBL1, DBC1*, *DGKZ*, *LRRFIP1*, *MDK*, *NOTCH4*, *PDC*, *PGBD1*, *PTBP2*, *SLCO6A1* or *UGT1*), their possible relationship to schizophrenia etiopathogenesis is still unknown. The data proceeding from GWAS studies provide evidence for suggesting that a number of chromosomal regions with common polymorphisms show genome-wide association with schizophrenia; however, they present only small odds ratios[8]. Past experiences suggest that for some disorders, as many as 20000 to 30000 case subjects and a similar number of comparison subjects are required to obtain highly robust findings[9]. This may be the arrangement in future SZ GWASs.

GENOMIC COPY NUMBER VARIATIONS

Recent genomic microarray technology has allowed genome-wide discovery of small deletions or duplications, known as copy number variations/variants (CNVs). The term "copy number variant" denotes a DNA sequence with a magnitude of 1 kb at least (by current convention), which is differently represented among individuals based on its deletion or duplication. CNVs are too small to be identified by standard karyotype. Most of the CNVs can be detected by the same technology which is used in genome-wide association studies[10]. CNVs are generated by diverse mutational mechanisms, including meiotic recombination, homology-directed and non-homologous repair of double-strand breaks, and errors in replications[11].

Copy number variations account roughly for 12% of human genomic DNA and each variation may range from one kilobase to several megabases in size. CNVs contrast with single nucleotide polymorphisms which affect only one single nucleotide base. CNVs may be inherited or caused by de novo mutation. CNVs can be limited to a single gene or include a contiguous set of genes. If a complete gene is affected by a duplication, the expression of the relevant protein can be increased. On the other hand, if a complete gene is lacking, the relevant protein is not synthetized at all[12]. The significance of microdeletions in schizophrenia etiopathogenesis was signalled long ago, when the 22q11.2 deletion syndrome (Velo-Cardio-Facial Syndrome) brings in a 20-fold increase in risk for schizophrenia[13].

According to a recent review, the CNVs at genome loci 1q21.1 (candidate gene *e.g., PRKAB2*), 2p16.3 (candidate gene *e.g., NRXN1*), 3q29 (candidate genes *e.g.,* BDH1, *DLG1*, *PAK2* or *TFRC*), 15q11.2 (candidate gene *e.g., CYFIP1*), 15q13.3 (candidate gene *e.g., CHRNA7*), 16p13.1 (candidate genes *e.g., NTAN1* or *NDE1*) and 22q11.2 (candidate genes *e.g., COMT*, *GSTT2* or *PRODH*) were associated with schizophrenia most frequently[14]. The data provide evidence for low prevalent (< 1%) but high penetrant CNVs associated with schizophrenia. CNVs may involve multiple genes and/or regulatory regions. CNV deletions show higher penetrance than duplications. Larger CNVs (> 100 kb) often have higher penetrance than smaller CNVs[15]. Although the vast majority of CNVs are inherited, CNVs that have newly occurred as de novo (spontaneous) mutations have more readily been implicated in diseases. *De novo* CNVs may be responsible for the presence of schizophrenia in only one of two monozygotic twins, who otherwise have identical genomes[16]. The explanation of the biological significance of CNVs, whether a deletion or a duplication, could be that the "dosage" of gene expression is tightly controlled during neurodevelopment and that the abnormalities of levels of gene expression, too much or too little transcription of a given gene, can perturb brain

development and lead to neurodevelopmental disorders. The increases in gene dosage may be less deleterious than the decreases[17].

ENDOPHENOTYPES IN GENETIC STUDIES OF SCHIZOPHRENIA

GWASs and studies of DNA microdeletions/microduplications help us to find genes and their polymorphisms that are important in schizophrenia etiology, yet the findings do not clarify schizophrenia pathogenesis. That is why genetic research of schizophrenia endophenotypes has recently been emphasized. The useful criteria for the identification of endophenotypes in psychiatric genetics has been postulated by Gottesman and Gould and supplemented by Gottesman *et al*[18] and Leboyer *et al*[19]: (1) The endophenotype is associated with illness in the population; (2) The endophenotype is heritable; (3) The endophenotype is primarily state-independent (manifests in an individual whether or not illness is active); (4) Within families, endophenotype and illness co-segregate; and (5) The endophenotype found in affected family members is found in non-affected family members at a higher rate than in the general population.

Neurophysiological (prepulse inhibition of the startle response, P50 suppression, P300 event-related potential, mismatch negativity), neuromotoric (smooth-pursuit eye movement, antisaccade task), neurocognitive (continuous performance task, span of apprehension, visual backward masking, Wisconsin card sorting test, verbal declarative memory), neuroanatomical (gyrus frontalis interior, gyrus temporalis superior, total brain volume, white brain matter connectivity), neurological (neurological soft signs) and personality (schizotypy, openness to experience) endophenotypes are studied in schizophrenia most frequently[20].

Imaging genetics of schizophrenia, as recently reviewed by Meyer-Lindenberg[21], represents a progressive approach to discovery of genetic background of neuroanatomical endophenotypes[]. The catechol-*O*-methyltransferase (*COMT*) gene has been the most-studied gene in schizophrenia imaging. The effects of genetic variation in *COMT* (rs4680 val/met polymorphism) are more consistent in functional findings compared to brain structure assessments. *e.g.*, de Frias *et al*[22] tested the tonic-phasic dopamine hypothesis by dissociating sustained and transient brain activity during performance on a 2-back working memory test using mixed blocked/event-related functional magnetic resonance imaging in 11 met/met and 11 val/val male carriers recruited from a random sample of the population. No differences in 2-back performance between genotype groups were found, but the met carriers displayed a greater transient medial temporal lobe response in the updating phase of working memory, whereas val carriers showed a greater sustained activation of the prefrontal cortex in the maintenance phase. These results support the tonic-phasic theory of dopamine function in the phenotypic influence of the COMT val(158)met polymorphism on different components of working memory, which is frequently impaired in schizophrenia[22]. *DRD2*, *DRD4*, *DAT1*, *RGS4* or *PPP1R1B* are other dopaminergic genes investigated in schizophrenia imaging. These studies provide strong support for the prefronto-neostriatal system as a core circuit for dopaminergic variation related to schizophrenia risk[21]. Interactions between genes (epistasis), CNVs and discovery science using imaging genetics are three of the research frontiers in imaging genetics of schizophrenia. In summary, the results especially related to lateral prefrontal cortex and subcortical structures (striatum, hippocampus) highlight a core neural system for genetic risk for schizophrenia.

According to Braff *et al*[23] researchers still face many problems related to genetic investigation of schizophrenia endophenotypes. Almost none of the recently described endophenotypes completely fulfils general criteria for endophenotypes. Genetic background of some endophenotypes may be complex and thus less attainable for research. Endophenotypes and their occurrence may be different in individual schizophrenia subtypes, especially in deficit *vs* non-deficit schizophrenia.

On the other hand, research of schizophrenia endophenotypes and their genetic background allows us to dissect complex clinical and etiopathogenetical characteristics of schizophrenia into simpler and better understandable sub-units and so reveal schizophrenia pathogenesis step by step.

DISCUSSION

A major limitation in genetic research is that clinical heterogeneity is typical in schizophrenia. Schizophrenia is not a disease but a cluster of clinical symptoms. No biological marker is involved in schizophrenia diagnostics at present. This means that very few schizophrenia patients probably share identical genomic causation.

The complex genetic architecture of the phenotype is another problem. Some genes may be disease-causing, whilst others only disease-modifying and thus less significant[24].

Many genetic findings are non-specific. Similar predisposing genes can be found across a number of psychiatric disorders. A notable finding is the overlap of susceptibility between schizophrenia and bipolar disorder for several individual risk alleles[25]. Population studies support this, *e.g.*, the association of polymorphisms in the genes for calcium and potassium channels in the central nervous system with the genetic risk for bipolar disorder as well as schizophrenia[26]. From this point of view, a quantitative dimensional approach to the assessment of individual clinical symptoms of mental disorders seems to be more valuable than the use of current psychiatric diagnoses. In schizophrenia, negative, delusional, depressive, manic, hallucinatory and disorganisation factor dimensions can be applied[27].

Further limitation is that rare variants with a 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[28].

Susceptibility for schizophrenia involves a complex interplay of both common (SNPs) and rare (CNVs) genetic risk variants. Because the common risk alleles individually have small effects on risk, collectively more than 70 identified common risk loci from GWAS may explain < 5% of the total genetic variance in schizophrenia susceptibility. The CNVs have much larger effects (odds ratio = 2-30) but are individually rare and are likely to make an even smaller contribution to the total risk. Genetic etiology of schizophrenia is complex and recently only partially resolved[29].

Genes themselves are not sufficient to induce schizophrenia; they also interplay with the environment (maternal pregnancy complications, prenatal maternal infection, abuse during childhood, urban environment, cannabis use, stressful life events *etc.*). This means that it is also necessary to study gene-environment interactions. As for the effect of cannabis in first episode schizophrenia, COMT, CNR1, BDNF, AKT1 and NRG1 are the most promising genetic variants interacting with cannabis exposure[30,31]. Nevertheless, not all these findings have been replicated.

On the other hand, the advantage of GWAS and studies of CNVs is that they may be based on a hypothesis-free genome-wide approach. GWAS, studies of CNVs and genetic research into schizophrenia endophenotypes do not compete but rather complement each other. The genes relevant for schizophrenia etiology may be discovered by GWAS and CNVs studies at first. Subsequently, the researchers will be able to find the matching neurobiological pathways in schizophrenia pathogenesis by the genetic research of endophenotypes.

Last but not least, there is a pressing need for better integration of the multiple research platforms in schizophrenia genetics, including biology computational models, epigenetics, transcriptomics, proteomics, metabolomics, neuroimaging and clinical correlations[32].

CONCLUSION

Looking for causes of schizophrenia, including the genetic ones, belongs to the most ambitious goals in modern psychiatry and will still probably continue to be so in the following decades. A better knowledge of the genetic background of schizophrenia can lead to changes in the treatment, prevention and genetic counselling helpful to the patient, family and clinicians. It may also reduce stigma in this severe mental disorder.

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