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Research Article

Transcription Factors in Schizophrenia: A Current View of Genetic Aspects

Abstract

Background: Schizophrenia is a polygenic mental disorder with about 80% heritability. Growing evidence indicated that synaptic dysfunctions contribute to SCZ etiopathogenesis.

The context and purpose of the study: Transcription factors play an important role in the regulation of gene expression. Whereas expression analysis of transcription factor has been performed, studies of their genetic variants are limited. The current review article summarizes data on transcription factors early growth response 3 (*EGR3*), c-fos transcription (*FOS*), immune early response 5 *(IER5)*, c-jun *(JUN),* Nk2 Homeobox 1 *(NKX2-1),* and transcription factor 4 *(TCF4)* encoding genes in schizophrenia.

Results and main findings: An important role of the mentioned genes in this pathology has been identified.

Conclusions: We concluded that the genetic variants of the transcription factor encodng genes might contribute to the assessment of disease susceptibility and can find potential use for the development of genetically-driven diagnostic approaches in the future.

Abbreviations

EGR3: Early Growth Response 3 Encoding Gene; FOS: C-Fos Transcription Factor Encoding Gene; IER5: Immune Early Response 5 Transcription Factor Encoding Gene; JUN: C-Jun Transcription Factor Encoding Gene; NKX2-1: Nk2 Homeobox 1 Encoding Gene; PCR-SSP: Polymerase Chain Reaction with Allele-Specific Primers; SCZ: Schizophrenia; TCF4: Transcription Factor 4 Encoding Gene

Background

Schizophrenia is a polygenic mental disorder with the estimated prevalence of 1% in general population and high heritability up to 80% [1]. Despite the results from a number of genome-wide and genetic association studies performed indicating an important role of several genes involved in immune response, neuronal development, apoptosis [2-6], the vast majority of heritable factors is still unclear. Transcription factors and their genetic variants are of special interest in the temrs of genetic component of schizophrenia development. It is well known that transcription factors are essential regulators of gene expression, and perform their function due to specific interaction with transcription factor binding sites located in the promoter region [7]. So far, Maurano et al. (2012) has shown that common single nucleotide polymorphisms (SNPs) are systematically enriched in transcription factor binding sites, especially, those active during fetal development [8]. While expression levels of some transcriptions factors have been partly studied [9-11], their genetic variants are relatively less studied in terms of schizophrenia [12].

The present review summarizes current findings concerning transcription factors in the pathogenesis of schizophrenia at both molecular and genetic levels.

Materials and Methods

An electronic literature search of peer-reviewed English language articles focused on transcription factors and schizophrenia using Pubmed was undertaken.

Transcription factor 4 (TCF4) in schizophrenia

Transcription factor 4 (TCF4, GeneBank ID: 6925) belongs to the superfamily of basic Helix-Loop-Helix (bHLH) transcription factors which acts as a transcriptional repressor or activator of gene expression [13]. A recent genome-wide association study has identified that *TCF4* is located in the

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genetic region considered as a risk factor for schizophrenia [14]. Animal studies suggested that *Tcf4*-deficient mice demonstrate abnormal brain development suggestting that *TCF4* gene expression might also affect brain networks involved in the cognitive functioning and processing [14]. In order to evaluate the potential association of genetic polymorphisms of *TCF4* with cognitive deficit in schizophrenia, Hui et al., (2015) performed a case-control study in Han Chinese population [15]. Assessment of disease symptoms using the Positive and Negative Syndrome Scale (PANSS) and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) suggested that a allele of the *TCF4* gene rs2958182 single nucleotide polymorphism (SNP) is a risk allele of schizophrenia, and is associated with lower cognitive performance in schizophrenia patients as well as delayed memory in controls [15]. By contrast, the earlier study performed in the same population has identified T allele as being associated with better performance of cognitive tasks in patients with schizophrenia but with worse performance in controls [16]. The results from expression analyses showed that mRNA expression level of *TCF4* is elevated in neurons derived from human-induced pluripotential stem cells of schizophrenia patients compared to those in healthy subjects [17]. Concerning the relevance to clinical symptoms, a recent pharmacogenetic study has revealed that TCF4 does not affect the improvement of disease symptoms during the treatment with antipsychotics [18]. However, it has been shown that the carriers of disease-associated *TCF4* gene rs9960767 allele had better recognition and information processing skills [18] suggesting an important contribution of TCF4 to the pathogenesis of schizophrenia.

Early growth response 3 (EGR3) in schizophrenia

Early growth response 3 gene (*EGR3*, GeneBank ID: 1960) encodes a transcriptional regulator belonging to the EGR family of CysCysHisCys (C2HC)-type zinc-finger proteins. It has been shown that *EGR3* is an immediate-early growth response gene and participates in the transcriptional regulation of genes involved in biological rhythm control. A variety of functions of *EGR3* such as participation in lymphocyte development, endothelial cell growth and migration as well neuronal development including regulation of synaptic proteins and synaptic plasticity has been shown [19,20]. Together with other immediate early gene transcription factors, EGR3 is activated in the brain in response to environmental stimuli and regulate downstream neuronal gene expression [20,21].

Genetic association studies performed in different populations have demonstrated important role of *EGR3* gene SNPs in the pathogenesis of schizophrenia [22-25]. Results from the Japanese study confirmed for 1140 independent case-control samples demonstrated that IVS1+607(A/G) (rs35201266) SNP has the strongest evidence for disease association [22]. Kim et al., (2010) reported that among the four examined SNPs of the *EGR3* gene the rs35201266 has a significant association with schizophrenia [23] that is in concordance with the previously reported data for the same population [22]. Moreover, it has been shown that the "T-G-C-G" haplotype of the rs1008949, rs7009708, rs35201266, and rs3750192 SNPs is overrepresented in patients with schizophrenia compared to controls [23]. A meta-analysis performed by Zhang et al., (2012) revealed a statistically significant association between schizophrenia and rs35201266 polymorphism of the *EGR3* gene [24]. Later, Nishamara et al., (2014) has provided *in vivo* human evidence of a significant effect of the *EGR3* gene polymorphisms (namely, rs35201266) on prefrontal hemodynamic activation level in healthy adults and schizophrenia patients. These data suggest that *EGR3* may affect prefrontal function through neurodevelopment [20]. So far, in a pooled study of biological pathways of schizophrenia risk it has been shown that the *EGR3* gene rs1877670 SNP is associated with disease [25]. Further, Willams et al., (2012) using a pharmacological approach has found that the locomotor suppressive effects of clozapine in Egr3(-/-) deficient mice is specific to second-generation antipsychotics while the first-generation medications suppress the locomotor activity of Egr3(-/-) and wild type mice to a similar degree [26]. Moreover, as the deficit in cortical serotonin 2A receptor (5HT(2A)R) in Egr3(-/-) mice aligns with reports on decreased 5HT(2A)R levels in the brains of schizophrenia patients suggesting a potential mechanism by which putative dysfunction in EGR3 in humans might affect the risk of schizophrenia development [26].

Nk2 Homeobox 1 (NKX2-1) gene in schizophrenia

Nk2 Homeobox 1 gene (*NKX2-1*, GeneBank ID: 7080) encodes a protein also known as a thyroid-specific transcription factor which binds to the thyroglobulin promoter and regulates the expression of thyroid-specific genes and those relevant to somatic symptoms common for schizophrenia [27]. NKX2-1 also plays a central role in the neurodevelopment and is essential for the formation and function of subgroups of neurons, glia, and functional neural networks affected in schizophrenia. It is well known that NKX2-1 expressing striatal GABAergic interneurons mainly contain parvalbumin (PV) [28] and it has been suggested that striatal PV+ interneurons play an important role in the behavioral effects mediated by antipsychotic drugs [29]. Moreover, a number of mice studies confirm the influence of striatal PV+ interneurons on schizophrenia [30,31]. This transcription factor also interacts with several susceptibility genes for schizophrenia, and is involved in gene-environment interactions with neurodevelopmental implications. Findings from families affected by inactivating mutations in *NKX2-1* suggested that they may result in brain-lung-thyroid disease, also known as benign hereditary chorea, characterized by impaired coordination, delayed speech development, neonatal pulmonary distress, and congenital hypothyroidism [32].

Myelin transcription factor 1-like (MYT1L) gene in schizophrenia

The myelin transcription factor 1-like gene (*MYT1L*, GeneBank ID: 23040) coding protein regulates proliferation and differentiation of oligodendrocytes and neural transcription [33,34]. Romm et al. (2005) has found that MYT1L is mainly expressed in the developing central nervous system (CNS) [34]. Among other pathologies, rare genetic variations of this

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gene have been linked to schizophrenia as well [35]. Later, Li et al., (2012) has examined six SNPs of the *MYT1L* gene in a Han Chinese population and has found that the rs17039584 polymorphism significantly associates with schizophrenia [36]. Up to date, there is lack of data suggesting implication of *MYT1L* gene SNPs in pharmacogenetics of schizophrenia; however, functions of the corresponding protein imply its putative significance in the terms of this disease.

Transcription factors cFos, cJun, and Ier5

Transcription factors cFos, cJun, and Ier5 participate in the regulation of numerous processes in human and higher animals, including those associated with neuronal plasticity and immune response. It has been shown that cFos is directly involved in learning and memory mechanisms and the lack of the cFos encoding gene in mice leads to impaired the long-term memory and synaptic transmission [37], the functional activity of which is also usually altered in schizophrenia [38]. Besides, cFos mediates cell response to mitogenic signals, which play a central role in neuron growth and differentiation, as well as in the formation of neural networks [39], typically altered in schizophrenia [40-42]. Experimental data from animal models of schizophrenia also suggest that FOS variants may contribute to the pathogenesis of schizophrenia [43-45]. Thus, it has been shown that *fos* gene expression is associated with significant weight gain [46].

Transcription factor AP1 formed by these two interacting proteins [47] enhances the transcription of genes the products of which are involved in a number of processes, including the formation of neuronal plasticity and longterm memory [48,49]. AP1 participates in the biogenesis of synaptic vesicles [49], in the assembly of their membranes [40], in the receptor transfer to dendrites [41] as well as controls cell differentiation, proliferation, and apoptosis [42]. Impaired functional activity of AP1 was observed in different diseases of the CNS, brain damage, cognitive deficit, and aging [43-46]. Postmortem brain studies showed that patients with schizophrenia had elevated FOS and JUN RNA levels in the thalamus, the structure that performs processing and integration of nearly all signals that the cortex receives the spinal cord, the midbrain, the cerebellum, and basal ganglions of the brain [47]. AP1 and cFos are also involved in the regulation of immune response: AP1 mediates the expression of proinflammatory cytokines [48], while cFos regulates cytokine expression by mast cells [49].

Up to date, there is lack of information concerning the role of the genetic variants of these transcription factors in schizophrenia. Moreover, no pharmacogenetic approach was used to study the effect of antipsychotic medications depending on the *FOS*, *JUN*, and *IER5* genetic variants. Our recent findings have identified three genetic variants associated with susceptibility to disease [50]. Thus, we have found that the *FOS* rs1063169, FOS rs7101, *JUN* rs11688, and *IER5* rs6425663 polymorphisms were associated with schizophrenia. In particular, the risk of schizophrenia was decreased in carriers of the minor alleles FOS rs1063169*T, JUN rs11688*A, and IER5 rs6425663*T, but increased in carriers of the FOS rs7101*T minor variant, especially in homozygotes [50].

Conclusion

This paper suggested the important role of transcription factors in the pathogenesis of schizophrenia. Based upon current findings we may suppose that as the most important players in the genetics of schizophrenia could be nominated transcription factors TCF4, EGR3, NKX2-1 as well as FOS, JUN, IER5 because SNPs in these genes are associated either with disease or its symptoms. However, the limited findings on genetics available nowadays in the terms of this pathology indicated the need of more investigations with s special focus on genetics. Only with specific focus on pharmacogenetic relevant genetic variants of transcription factors it would become possible to uncover disease-associated SNPs and develop genetically-driven diagnostic and prognostic approaches.

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