changes in DISC1 mRNA impact on protein expression and are specific for brain regions and psychotropic drugs. It also should be noted that we measured expression only of the common transcript for both of these genes. It is not currently known whether schizophrenia involves alternate processing of these genes into disease related transcripts or isoforms and we cannot rule out that treatment may impact on variable splicing or processing of these genes.

A balanced translocation in the DISC1 gene segregates with schizophrenia and other major psychiatric illnesses in a Scottish family (Millar et al., 2000). However, little is known about how the translocation affects the expression and/or function of the DISC1 gene. DISC1 protein expression in lymphoblasts derived from the family member with the translocation was observed to be decreased but the mutant truncated form of DISC1, which should be produced by the translocation, was not found (James et al., 2004). It is unknown whether the expression of DISC1 in brains of the family members is altered or not, however, this observation in peripheral cells suggested that the translocation might decrease the expression of DISC1. Alternatively, mutant truncated form of DISC1, which has been shown to play a role in inhibiting neurite outgrowth (Ozeki et al., 2003), might down-regulate the DISC1 protein expression and/or function. These findings suggest that reduced expression of DISC1 in brain might be expected in schizophrenic brain if DISC1 is involved in the pathogenesis of schizophrenia. On the other hand, gross expression levels of DISC1 protein have not been found to be changed in frontal cortex in patients with schizophrenia (Sawamura et al., 2005) and expression levels of DISC1 mRNA tended to be increased in hippocampus of schizophrenia patients (Lipska et al., 2004). Our data suggest that increased expression of DISC1 mRNA may be, at least in part, related to treatment with some atypical antipsychotics.

Evidence that dysbindin is associated with schizophrenia is now quite strong, although no functional mutation in dysbindin gene has yet been identified. Recent postmortem studies have found decreased expression of dysbindin mRNA and protein in hippocampus and frontal cortex in schizophrenic patients (McClintock et al., 2003; Talbot et al., 2004; Weickert et al., 2004). In contrast to our data with DISC1, we found no consistent pattern of altered dysbindin expression in hippocampus and frontal cortex following antipsychotic treatment.

Knowledge about protein functions of DISC1 and dysbindin is insufficient, however, we discuss a possibility how these genes affect the mechanisms of schizophrenia. As DISC1 has a prominent role in the neurite extension and its expression is developmentally regulated (Ozeki et al., 2003), upregulation of DISC1 could support the maturation of dendritic spine, which is believed to be affected in schizophrenia. As dysbindin promotes glutamate release in neuronal culture (Numakawa et al., 2004), reduced expression of dysbindin in schizophrenic brain could be relevant to glutamatergic dysfunction, which has been implicated in the pathophysiology of schizophrenia.

In summary, our findings offer preliminary evidence that altered expression of DISC1 may be caused by certain antipsychotic drugs, suggesting a role for DISC1 in therapeutic actions of these drugs. Additional studies are warranted to examine DISC1 and dysbindin expression, including western blotting analysis, in situ hybridization, immunohistochemistry, and the effect of other psychotropic drugs.

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Possible association between nonsynonymous polymorphisms of the anaplastic lymphoma kinase (ALK) gene and schizophrenia in a Japanese population

Short Communication

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Summary. We examined, for the first time, the possible association between schizophrenia and the anaplastic lymphoma kinase (ALK) gene which plays an important role in neurodevelopment. When two nonsynonymous polymorphisms (Arg1491Lys and Glu1529Asp) were examined, there were significant differences in genotype and allele distributions between patients and controls. Individuals homozygous for the minor allele (1491Lys–1529Asp) were more common in patients than in controls ($p = 0.0064$, odds ratio 2.4, 95% CI 1.3–4.6). These results suggest that genetic variations of the ALK gene might confer susceptibility to schizophrenia.

Keywords: Schizophrenia, anaplastic lymphoma kinase (ALK), single nucleotide polymorphism (SNP), association, susceptibility.

Introduction

Growing evidence has suggested that alterations of neurotrophic factors may be involved in the morphological, cytoarchitectural and neurobiochemical abnormalities in the brain of schizophrenic patients (Thome et al., 1998; Durany and Thome, 2004). Anaplastic lymphoma kinase (ALK) was originally identified as an oncogene activated in anaplastic large cell lymphomas with chromosomal translocation t (2;5) (Morris et al., 1994; Shiota et al., 1994). Subsequent cloning of the ALK gene revealed that it encodes a receptor-type protein tyrosine kinase (RTK) of the insulin receptor family (Iwahara et al., 1997; Morris et al., 1997). Neurotrophic factors exert their effects through binding to RTKs and play an important role in neurodevelopment such as

differentiation, proliferation, survival, and synaptic formation. Indeed, ALK was found to be a receptor for heparin-binding growth factors, midkine (Stoica et al., 2002) and pleiotrophin (Stoica et al., 2001). Midkine and pleiotrophin show approximately 50% identity in amino acid sequence and share the same genomic organization. These proteins play an important role in early neurogenesis, neurite outgrowth, nerve cell migration, and neuroprotection (reviewed by Kadomatsu and Muramatsu, 2004). Of note, a recent study reported alterations in serum midkine levels in patients with schizophrenia (Shimizu et al., 2003).

ALK is expressed almost exclusively in perinatal neural cells. In the central nervous system, it is highly expressed in diencephalons, midbrain, and the ventral half of the spinal cord. After birth, its expression decreases; however, it persists to be expressed in some regions such as the thalamus, olfactory bulb, and midbrain (Iwahara et al., 1997). These brain regions have been implicated in the pathophysiology of schizophrenia (e.g., Moberg and Turetsky, 2003; Clinton and Meador-Woodruff, 2004). The ALK gene is, therefore, a good candidate gene for association analysis with schizophrenia. To our knowledge, however, there is no study examining the possible association between the ALK gene and schizophrenia. The ALK gene maps to chromosome 2p23 (Morris et al., 1994). We searched for nonsynonymous single nucleotide polymorphisms (SNPs) in the ALK gene *in silico* and found only 2 common SNPs which have been well validated: a nucleotide substitution (G>A: NCBI SNP ID rs1881420) resulting in an amino acid change of Arg1491Lys (amino acid numbering is according to NCBI protein data base accession NP_004295) and G>C (rs1881421) resulting in Glu1529Asp. Since these polymorphisms may alter functions of ALK protein, we performed an association study between these polymorphisms and schizophrenia.

Materials and methods

Subjects

Subjects were 300 patients with schizophrenia (154 males, mean age of 45.3 years [SD 14.3]) and 308 healthy controls (140 males, 39.8 years [SD 11.5]). All subjects were biologically unrelated Japanese and recruited from the same geographical area (Western part of Tokyo Metropolitan). Consensus diagnosis by at least two psychiatrists was made for each patient according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria (American Psychiatric Association, 1994) on the basis of unstructured interviews and information from medical records. The controls were healthy volunteers recruited from hospital staffs and their associates. They were interviewed and those individuals who had current or past history of psychiatric treatment were not enrolled in the study.

The study was performed in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). After description of the study, written informed consent was obtained from every subject. The study protocol was approved by the ethics committees at the Showa University School of Medicine and the National Center of Neurology and Psychiatry, Japan.

Genotyping

Venous blood was drawn from the subjects and genomic DNA was extracted from whole blood according to the standard procedures. The index SNPs (rs1881420 and rs1881421) were genotyped using the TaqMan 5′-exonuclease allelic discrimination assay, as described previously (Hashimoto et al., 2004, 2005). Primers and probes for detection of the SNPs were as follows: 5′-TTCTCTCAGTCCAACCCTCCTT-3′ (forward primer), 5′-CTGGTGGGCTTGTTTCTGGAT-3′ (reverse primer), 5′-VIC-TTGCACAAGGTCCAC-MGB-3′ (probe 1), and 5′-FAM-TGCACAGGGTCCAC-MGB-3′ (probe 2) for rs1881420; 5′-AGAGAAACCC ACCAAAAAGAATAATCCT-3′ (forward primer), 5′-GTTAGGTGGGACAGTACAGCTT-3′ (reverse primer), 5′-VIC-CAGGTTACCCCTGTCGTGT-MGB-3′ (probe 1), and 5′-FAM-CAGGTTACCCCTCTCGTGT-MGB-3′ (probe 2) for rs1881421. Thermal cycling for polymerase chain reaction (PCR) were 1 cycle at 95°C for 10 minutes followed by 50 cycles of 92°C for 15 seconds and 60°C for 1 minute. Genotype data were read blind to the case-control status.

Statistical analysis

The presence of Hardy-Weinberg equilibrium was examined by using the χ^2 test for goodness of fit.

Table 1. Genotype distributions and allele frequencies of the Glu1529Asp polymorphism of the ALK gene (rs1881421) in patients with schizophrenia and controls

	Genotype distribution				Allele frequency	
	N	Glu/Glu	Glu/Asp	Asp/Asp	N	Glu	Asp
Patients	300	141 (47%)	128 (43%)	31 (10%)	600	410 (68%)	190 (32%)
Controls	308	171 (55%)	123 (40%)	14 (5%)	616	465 (75%)	151 (25%)

Genotype and allele distributions were compared between patients and controls by using the χ^2 test for independence. All p-values reported are two-tailed.

Results

Nearly all the subjects except for three (99.5%) had the same genotype for the two SNPs of rs1881420 and rs1881421, i.e., genotypes of G/G, G/A, and A/A in the former corresponded to those of G/G, G/C, and C/C in the latter. Thus, we show results of statistical analyses for the SNP rs1881421 (Glu1529Asp) only. Genotype distributions and allele frequencies in patients and controls are shown in Table 1. The genotype distribution was not significantly deviated from Hardy-Weinberg equilibrium for patients and controls (patients: $\chi^2 = 0.1$, df = 1, p = 0.81; controls: $\chi^2 = 1.9$, df = 1, p = 0.16). There was a significant difference in the overall genotype distribution between patients and controls ($\chi^2 = 9.3$, df = 2, p = 0.0095). Individuals homozygous for the minor allele (1529Asp) was significantly more common in patients than in controls ($\chi^2 = 7.4$, df = 1, p = 0.0064, odds ratio 2.4, 95% CI 1.3–4.6). When allele frequencies were compared, the 1529Asp allele was significantly more frequent in patients than in controls ($\chi^2 = 7.7$, df = 1, p = 0.0055, odds ratio 1.4, 95% CI 1.1–1.8).

Discussion

We examined, for the first time, the possible association between schizophrenia and the anaplastic lymphoma kinase (ALK) gene which plays an important role in neurodevelopment such as early neurogenesis, neurite outgrowth, nerve cell migration, and neuroprotection. We found that the minor allele (1529Asp) of the Glu1529Asp polymorphism (rs1881421) and homozygosity for this allele were significantly more common in patients with schizophrenia than in controls. Since nearly all the subjects had the same genotype for the other SNP, Arg1491Lys (rs1881420), the risk alleles constitute a haplotype 1491Lys–1529Asp. Thus, our results suggest that the 1491Lys–1529Asp haplotype or its homozygosity may confer susceptibility to schizophrenia. However, we do not know whether these nonsynonymous polymorphisms do alter functions of the ALK protein to give susceptibility to schizophrenia. Accordingly, there remains a possibility that other polymorphisms, which are in linkage disequilibrium to these polymorphisms, are truly responsible for giving susceptibility.

The ALK gene encodes a 1620 amino acid protein containing a putative 26 amino acid signal peptide, an extracellular domain of 1004 amino acid after signal peptide cleavage, a transmembrane domain of 28 hydrophobic amino acids, a juxtamembrane segment of 64 amino acids, a catalytic domain (protein tyrosine kinase domain) of 254 amino acids, followed by the carboxyl-terminal tail of 244 amino acids (Morris et al., 1997). The Arg1491Lys and Glu1529Asp residues lie close to a NPTY motif (residue 1504–1507) in the carboxyl-terminal tail (Morris et al., 1997). Such motifs mediate the interaction of RTKs with signaling substrates such as the insulin receptor substrate-1 and Src homology

and collagen proteins through the substrates's phosphotyrosine binding (PTB) domain (van der Geer and Pawson, 1995). It is possible that amino acid changes of Arg1491Lys and Glu1529Asp may alter protein structure and affect functions (e.g., binding to these substrates).

ALK is a receptor-type protein kinase (RTK) that is expressed preferentially in neurons of the central and peripheral nervous systems at late embryonic stages (Iwahara et al., ■; Morris et al., 1997). Neurotrophic factors exert their effects through binding to RTKs, and ALK is a receptor for heparin-binding growth factors, midkine and pleiotrophin (Stoica et al., 2001, 2002). Thus it is likely that ALK play an important role in neurodevelopment such as differentiation, proliferation, survival, neurite outgrowth and synaptic formation, and alterations of ALK functions may result in vulnerability to developing schizophrenia, which accords with the neurotrophic factor theory of schizophrenia (Thome et al., 1998; Durany and Thome, 2004). Indeed, alterations in other neurotrophic factors such as brain-derived neurotrophic factors (BDNF) and neurotrophin-3 have been implicated in schizophrenia (e.g., Durany et al., 2001; Nanko et al., 2003; Hattori et al., 2002).

A limitation in the present study might be that the obtained evidence for association was not very strong (p-values of <0.01 level in a single sample). Replication studies in independent samples are required. If our results are replicated, experiments elucidating the possible effects of the amino acid substitutions (Arg1491Lys and Glu1529Asp) on the ALK protein functions may serve to advance our understanding of the molecular mechanisms of schizophrenia and may provide clues to production of new treatment of the illness.

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Susceptibility genes for schizophrenia

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Key Words: schizophrenia, susceptibility gene, dysbindin, neuregulin-1, DISC1, COMT, G72, RGS4, Akt

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Abstract

It is well known that genetic factors contribute to the susceptibility for schizophrenia. Recent advance of the molecular genetics of schizophrenia strongly suggests several susceptibility genes, e.g. dysbindin, neuregulin-1, DISC1, COMT, G72, RGS4 and Akt1. We discuss the evidence and biology of these genes. As glutamate transmission is especially implicated in these genes, neurobiological basis of schizophrenia might be elucidated by investigation of functional interactions between susceptibility genes for schizophrenia and glutamatergic system.

Introduction

Schizophrenia is a major mental disorder that is one of the world's top ten causes of long-term disability. This disease is characterized by psychosis and profound disturbances of cognition, emotion and social functioning. It affects approximately 1% of the general population across different countries and cultural group worldwide. The fact that schizophrenia has a genetic component has long been established with high heritability estimates of 80%[1, 2]. As the genetic transmission does not appear to follow simple mendelian single-gene inheritance pattern, this disease is a complex genetic disorder, like other common diseases. Many years of much effort has devoted to identify susceptibility genes for schizophrenia. As a result, genome wide linkage studies suggested several positive linkage regions such as 1q, 5q, 6p, 6q, 8p, 10p, 13q, 22q[3, 4]. A recent meta-analysis showed evidence for linkage at 8p, 13q and 22q[5], and another meta-analysis at 1q, 2p, 2q, 3p, 5q, 6p, 8p, 11q, 14q, 20p, 22q[6]. The chromosomal abnormalities in schizophrenia have also added the evidence for susceptibility loci at 1q42[7, 8] and 22q11[9-11]. A number of susceptibility genes for schizophrenia, including dysbindin, neuregulin-1, DISC1, COMT, and G72 and RGS4, have recently been identified in these loci[12-17]. The evidence for several genes becomes stronger now, as replication studies have achieved greater consistency than in the past[18]. Here we discuss the genetic evidence and biology of these susceptibility genes.

Dysbindin

A recent study implicated a gene on chromosome 6p, dysbindin (DTNBP1: dystrobrevin binding protein 1), as a susceptibility locus in the Irish pedigrees[12]. Since then, a significant association between schizophrenia and genetic variation in dysbindin has been reported in various populations from Ireland, Wales, Germany/Hungary/Israel, Sweden, Bulgaria, Unite States, China, and Japan[19-27]. One study, which initially failed to replicate a positive association based on SNPs in an Irish population, became subsequently positive using a haplotype strategy[28]. Thus, genetic evidence for association with schizophrenia is quite strong. Talbot et al.[29] found that dysbindin protein levels were reduced in the hippocampal formation of patients with schizophrenia. This presynaptic reduction was observed especially in the inner molecular layer of the dentate gyrus. The expression levels of dysbindin mRNA and protein were also reduced in the prefrontal cortex in schizophrenic brains[30, 31].

Dysbindin is originally found as a binding partner of alpha- and beta-dystrobrevins, which are causative genes of Duchenne muscular dystrophy [32]. Dystrobrevins are parts of the dystrophin-associated protein complex which plays important roles in normal function of muscle[33]. Cognitive impairments are commonly found in patients with Duchenne muscular dystrophy and it is thought to be due to an abnormality in the neuronal membrane that is caused by lack of dystrophin[34]. A model mouse of Hermansky-Pudlak syndrome, sandy mouse, is caused by a nonsense mutation in the dysbindin gene[35]. This disease is characterized by oculocutaneous albinism, prolonged bleeding and pulmonary fibrosis due to abnormal vesicle trafficking to lysosomes and related organelles[36]. Dysbindin is a component of the biogenesis of lysosome-related organelles complex (BLOC-1) and reduced expression of other proteins in this complex has been found in the sandy mouse[35]. Altered expression of dysbindin in schizophrenic brain might affect the expression of BLOC-1, which could result in the abnormal protein trafficking in schizophrenia. Although several findings of function of dysbindin have been

reported, little is known about the functions in neurons. Numakawa et al.[20] have recently shown that dysbindin might influence exocytotic glutamate release via up-regulation of the molecules in pre-synaptic machinery. They also reported that dysbindin promotes neuronal viability through PI3K-Akt signaling[20]. Impairments of these functions of dysbindin could play an important role in the pathogenesis of schizophrenia.

Neuregulin-1

Neuregulin-1 (NRG-1), which maps to the 8p locus, has been shown as a susceptibility gene for schizophrenia by a combination of linkage and association analysis[13]. Additional evidence for association with schizophrenia has been reported by ten independent groups[37-46], whereas three studies failed to replicate it[47-49]. Notably, the majority of positive markers are located at the 5' region of this gene, which is close to the first exons encoding type IV and type II of NRG-1. Quite strong evidence for association with schizophrenia is suggested. Hashimoto et al.[50] studied NRG-1 mRNA expression in dorsolateral prefrontal cortex (DLPFC) and found increased type I NRG1 mRNA in schizophrenia. The elevation of type I expression was present relative to three house keeping genes and to other NRG-1 isoforms (type II and type III). However, type I NRG1 mRNA expression levels correlated with neuroleptic doses in patients with schizophrenia, thus it is unclear this finding reflected a neuroleptic effect or disease severity. It is notable that Law et al.[51] replicated the increased mRNA expression of type I NRG-1 in a much larger and separate sample in hippocampus and did not find any correlation between medication and NRG1 mRNA.

NRG-1 is one of the neuregulin family of proteins, which have a broad range of bioactivities in the central nervous system and contain an epidermal growth factor (EGF)-like motif that activates membrane-associated tyrosine kinase related to ErbB receptors[52]. NRG-1 regulates the expression and plasticity of N-methyl-d-aspartate (NMDA) receptors, of the β2 subunit of the γ-amino butyric acid (GABA) receptor and of nicotinic acetylcholine receptor

subtypes including α5, α7 and β4 subunits[53-56]. A gene targeting approach for NRG-1-ErbB signaling revealed a behavioral phenotype in mice that overlaps with certain animal models for schizophrenia. For example, NRG-1 and ErbB4 mutant mice exhibit elevated activity levels in an open field, which was reversed by clozapine, and abnormal sensorimotor gating measured by prepulse inhibition of the startle reflex[13, 57]. The NRG-1 gene generates multiple alternative splicing variants, classified into three primary isoform groups (types I: heregulin / acetylcholine receptor inducing activity / neu differentiation factor, II: glial growth factor, III: sensory and motor neuron-derived factor)[58], and recently additional 5' exon containing transcripts (types IV, V, VI) have been found in human brain[59]. These NRG-1 isoforms play multiple and distinct functions in neuronal development, which may be relevant to neurodevelopmental abnormalities in schizophrenia.

DISC1

The Disrupted in Schizophrenia 1 (DISC1) gene has initially been identified at the breakpoint of a balanced translocation (1;11)(q42.1;q14.3), which segregates with schizophrenia and related psychiatric disorders in a large Scottish family[7, 14]. Five studies reported a significant association between schizophrenia and genetic variation in the DISC1 gene[60-64] and we also found such an association (Hashimoto et al., unpublished). However, two studies failed to find the association[65, 66]. There is evidence for association with bipolar disorder[62, 64] and with major depression (Hashimoto et al., unpublished). A frameshift mutation of the DISC1 gene has been found in an American family with schizophrenia and schizoaffective disorder[67]. These findings suggest that DISC1 may give a susceptibility to mood disorders as well as schizophrenia. The function of DISC1 is still unclear, however, increasing evidence suggests a role in cytoskeletal organization, as DISC1 interacting proteins are associated with the components of microtubule and actin[68-71]. DISC1 is likely to be involved in the neurite extension[68, 70] and mitochondrial and nuclear related functions have also been suggested[69, 72-74].

COMT

Catechol O-methyltransferase (COMT) is a susceptibility gene for schizophrenia, which maps to 22q11 implicated in two meta-analyses of linkage studies[5, 6]. Hemideletion of this region produces velo-cardio-facial syndrome (VCFS), a condition associated with increased risk of schizophrenia-like psychoses[75]. COMT is a key enzyme in the elimination of dopamine in the prefrontal cortex. A functional polymorphism of the COMT gene, Val158Met, affects prefrontal function, and the high-activity val allele has been reported to be a genetic risk factor for schizophrenia in at least eight studies[18]. Among the susceptibility genes for schizophrenia, only COMT has evidence for the association with functional polymorphism. As COMT val allele is associated with prefrontal abnormalities, COMT is linked more strongly with cognitive intermediate phenotypes, e.g. executive function, cortical processing and P300 evoked EEG response[15, 76, 77]. The mRNA expression levels of COMT in schizophrenia has been studied in DLPFC and they show only minor alterations[78, 79]. Many negative results have also been reported and recent meta-analysis was inconclusive[80], however, it is likely that the COMT Val158Met polymorphism is a part of the complex risk architecture of schizophrenia[18].

G72

G72 was cloned from a 5 MB gene desert in the 13q linkage region[16]. Biochemical study revealed that G72 protein activated D-amino acid oxidase (DAAO), which was involved in the metabolism of D-serine, an agonist at the glycine modulately site of the NMDA receptor[16]. Chumakov et al. also reported that DAAO was associated with schizophrenia[16]. Subsequently, five studies suggested a significant association between schizophrenia and G72[81-85], whereas one study did not support the association[86]. As the association with child-onset schizophrenia and with bipolar disorder has also been reported[83, 87, 88], this gene is likely to be a susceptibility gene for psychosis. The increased expression of G72 mRNA was observed in DLPFC of postmortem

brain in patients with schizophrenia, which is consistent with glutamatergic theory of schizophrenia.

RGS4

Regulator of G-protein signaling 4 (RGS4) has been discovered to be decreased in the prefrontal cortex of patients with schizophrenia using cDNA microarrays[17]. RGS4 maps to 1q, one of the suggestive linkage regions[3, 4, 6]. Five reports suggested the association with schizophrenia[89-93], while two studies failed to replicate it[94, 95]. RGS4 deficient mice showed normal behavior including intact prepulse inhibition, except subtle sensorimortor abnormality[96]. RGS4 accelerates the GTPase activities of G protein alpha-subunits and negatively modulates G protein–mediated signaling via dopamine, metabotropic glutamate, and muscarinic receptors. The evidence for genetic association between schizophrenia and RGS4 is suggestive.

Akt1

Akt1 (protein kinase B) is implicated as a susceptibility gene for schizophrenia using a combination of experiments[97]. Emamian et al.[97] reported reduced expression of Akt1 protein in lymphocytes and postmortem brain tissue of patients with schizophrenia and genetic association between Akt1 and schizophrenia. They also demonstrated higher sensitivity to amphetamine-induced PPI disruption in Akt1 knockout mouse[97]. Subsequent two studies supported the evidence for association of variants in the Akt1 gene with schizophrenia[98, 99], whereas one study failed to replicate it[100]. Akt has emerged as the focal point for many signal transduction pathways, regulating multiple cellular processes such as glucose metabolism, transcription, apoptosis, cell proliferation, angiogenesis, and cell motility[101]. In the central nervous system, the PI3K-Akt signaling pathway plays a critical role in mediating survival signals[102, 103]. PI3-kinase-Akt signaling is also involved in the survival promoting effect of dysbindin[20]. Despite weak linkage

evidence of Akt1 (14q) and small number of positive association studies, biological evidence strengthens the candidacy of Akt1 as a susceptibility gene for schizophrenia.

Conclusion

Several studies have replicated genetic association between polymorphisms in dysbindin, neuregulin-1, DISC1, COMT, G72, RGS4, and Akt1 and schizophrenia. However, no causative polymorphism has not been described in schizophrenia, except for the val allele in the COMT gene. Discovery of the causative mutation is the next step of this field. As biological evidence of these genes accumulates in the glutamate transmission, further investigations of functional connectivity among these susceptibility genes and glutamatergic system should be conducted.

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