The DISC1 genetic pathway and its role in Schizophrenia development

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Abstract

Schizophrenia is a severe mental disorder with a high heritability factor. Because of its early onset and high impact symptoms, it heavily affects the quality of life for the patient. Several mechanisms underlie the development of schizophrenia. Most of them involve cortical development. Here, some of the characteristic features of schizophrenia will be discussed. Next, one of the genes which is found to be related to schizophrenia, Disrupted In Schizophrenia 1 (DISC1), and its role in schizophrenia will be examined. However, the main focus will be on several other factors with which DISC1 interacts, and their possible role in schizophrenia. GSK3β, DIXDC1, NDEL1, LIS1, PCM1, BBS4, and APP all interact with DISC1 and are involved in cortical development. Of each factor, their function will be examined and how they might contribute to the development of schizophrenia. The conclusion drawn is that all these factors can play a role in the development of schizophrenia. Furthermore, defects in these targets might explain the broad diversity of DISC1 related defects which are related to schizophrenia. Therefore further research into these targets can be useful to get a better understanding of schizophrenia. Furthermore, the therapeutic value of this data will be discussed, which shows that usage of morpholino-oligonucleotides to specifically target DISC1 related defects might prove very successful

Introduction

Schizophrenia is a mental disorder with a heritable factor which manifests itself in multiple symptoms (Kas, et al., 2011). Symptoms include delusions, hallucinations, disorganized speech, disturbed psychomotor behavior, and negative symptoms such as avolition and lack of emotional reactivity. According to DSM-IV, two or more of these symptoms should be present to diagnose a patient with schizophrenia. In addition, these symptoms should be present for at least a month, if untreated (American Psychiatric Association, 2000). However, also different criteria for schizophrenia are used for its classification. Depending on which criteria are used, lifetime prevalence of schizophrenia is between 0.30 % - 0.66% and an incidence rate of 8-40 per 100000 person years (McGrath, Saha, Chant, & Welham, 2008; van Os & Kapur, 2009; Tandon, Keshavan, & Nasrallah, 2008). Often it is hard to discriminate between schizophrenia and other psychiatric disorders such as bipolar disorder because their symptoms overlap (Tandon, Keshavan, & Nasrallah, 2008). However, the impact of schizophrenia on a patient's life is generally severe because of the early onset of the disease and the large effect on the patient's general and social functioning. In addition, the disease is associated with significant increases in risk on suicide and a doubling of mortality related to age (Tandon, Keshavan, & Nasrallah, 2008; Pompili, Lester, Innamorati, Tatarelli, & Girardi, 2008; Lee, Ma, Yen, Huang, & Chiang, 2012). Furthermore, reduced rates of employment, increased numbers of homelessness and increased financial dependence were found in schizophrenic patients (Tandon, Keshavan, & Nasrallah, 2008).

Symptoms

Symptoms are usually classified into several categories, including, positive, negative, cognitive disorganization, mood, and motor symptoms. Positive symptoms contain distortion of sense of reality and include hallucinations, delusions and alike usually caused by dopaminergic mesolimbic hyperactivity. These positive symptoms can differ in severity and type. Moreover, these hallucinations can involve all types of sensory input, but auditory hallucinations are reported mostly. The onset of these positive symptoms usually occurs in early adulthood and is an important marker for schizophrenia (Tandon, Nasrallah, & Keshavan, 2009). In addition, patients suffering from schizophrenia often show a flattening of emotional responses and cognitive functioning, these are called negative symptoms. These symptoms consist of apathy, avolition, anhedonia, abulia, alogia and reduced social functioning and drive (Tandon, Keshavan, & Nasrallah, 2008). These negative symptoms can be induced directly as a consequence of the disrupted brain functioning or by external factors which are linked to schizophrenia such as depression, side effects of medication and others. Because the underlying mechanisms of these negative effects are not fully understood, treatment of these effects is not yet very effective (Tandon, Keshavan, & Nasrallah, 2008). However, schizophrenia

patients might also display an increase in emotional responsiveness. All these mood symptoms can co-occur with the formerly described positive symptoms (Aleman & Kahn, 2005). Depression is one of these mood symptoms found in most schizophrenia patients throughout different stages of schizophrenia. This depression strongly contributes to the decreased quality of life of schizophrenia patients (Potvin, Sepehry, & Stip, 2007; Tandon, Keshavan, & Nasrallah, 2008). Closely related to depression, is the variety of anxiety symptoms displayed in some schizophrenic patients especially in early stages of the disease. Hence, anxiety disorders are commonly found in schizophrenic patients (Tandon, Nasrallah, & Keshavan, 2009).

Another symptom of schizophrenia is cognitive disorganization. Because of this cognitive disorganization, patients are mildly to severely impaired in structuring their thoughts in to clear, logical thoughts focused on a goal. This disorganization of the thought processes can lead to disorganization in behavior. However, not much is known about the underlying mechanisms (Tandon, Keshavan, & Nasrallah, 2008; Tandon, Nasrallah, & Keshavan, 2009). In addition, a relatively high prevalence rate of disruption of motor functions is found in schizophrenia patients. These symptoms are probably related to a disruption in the development of the motor cortex (Walther & Strik, 2012). These symptoms manifest themselves in multiple ways, ranging from a general slowing down of motor activity to secluded expressions of abnormal motor activity (Walther & Strik, 2012; Docx, et al., 2012; Daniels, 2009). Signs of these motor disruptions are excitement, immobility, mutism, staring, posturing, grimacing, stereotypy, mannerisms, verbigeration, rigidity, negativism, waxy flexibility, echolalia, echopraxia and withdrawal (Daniels, 2009).

Virtually all schizophrenia patients suffer from some degree of cognitive impairment (Kitchen, Rofail, Heron, & Sacco, 2012; Tandon, Nasrallah, & Keshavan, 2009). Main affected cognitive functions are memory, attention, concentration, problem solving, learning, executive function, processing speed, and social cognition (Kitchen, Rofail, Heron, & Sacco, 2012). These cognitive symptoms are present already in the premorbid phase of schizophrenia and long lasting (Tandon, Nasrallah, & Keshavan, 2009). Treatment can reduce some of these cognitive impairments. However, little is known about the 'natural' (untreated) development of these symptoms over a patient's lifespan. The cognitive impairment contributes substantially to the burden of the disease (Kitchen, Rofail, Heron, & Sacco, 2012).

In some patients suffering from schizophrenia, minor physical abnormalities were found such as deformation of the palate, deformation of the skull, and others. Particular zones where these are found in schizophrenia patients are on the head, eyes, ears, mouth, hands and feet. Little is known about the exact cause of these abnormalities. They are probably produced during the first en second

trimester of gestation. These abnormalities might be used as markers for schizophrenia. Similar abnormalities have also been reported in related disorders such as autism (Franco, Valero, & Labad, 2010).

Different Stages of Schizophrenia

The course of schizophrenia over a patient's lifespan, if untreated, can be divided in several phases. The first phase is the premorbid phase, followed by a prodromal phase, a psychotic phase and ending with a stable phase (Fig. 1). The premorbid phase, which onset is during childhood, is not particularly remarkable except from some minor deficits in cognitive, motor, or social functioning. Examples of symptoms in this phase are, delayed motor development, attention deficits, learning deficits, social isolation, and emotional detachment (Tandon, Nasrallah, & Keshavan, 2009). During early adolescence the prodromal face commences. This phase is characterized by an increase in positive symptoms and functional decline. Most effort is put into identifying patients in this phase. The prodromal phase ends when the patients experiences a first psychotic episode which marks the initiation of the next phase, the psychotic phase (Yung & McGorry, 1996; Vaglum, 1996). In the psychotic phase the patients experience multiple psychotic episodes and other positive symptoms.

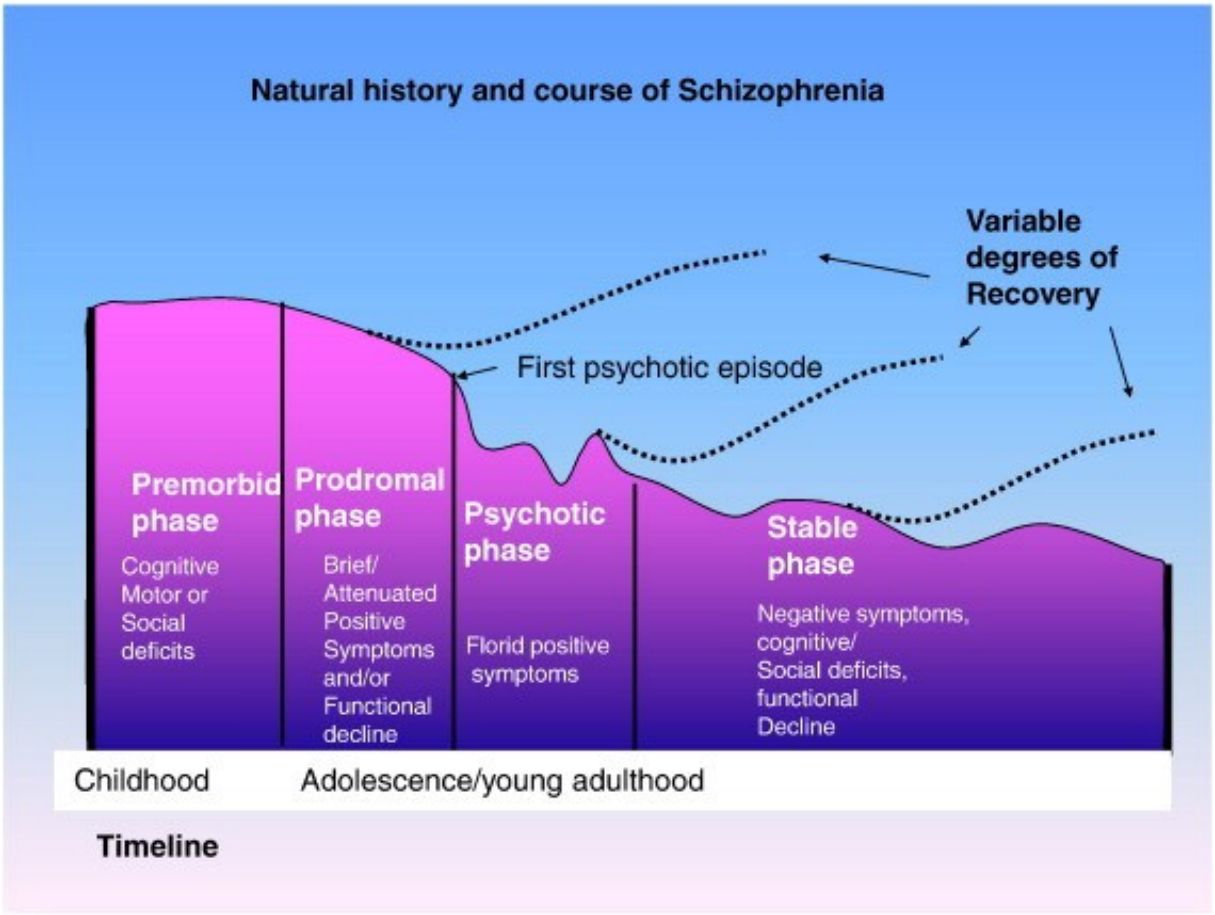

Fig. 1: the different phases and progressions of schizophrenia. (Tandon, Nasrallah, & Keshavan, 2009)

Between those psychotic episodes there are periods of remission. However, after these periods, the symptoms are usually worse than before (Tandon, Nasrallah, & Keshavan, 2009; Yung & McGorry, 1996). In time, the positive symptoms will decrease and negative symptoms will become more prominent. This marks the transition to the stable phase. This phase is mainly dominated by negative symptoms, cognitive and social functioning and a further decline (Yung & McGorry, 1996; Tandon, Nasrallah, & Keshavan, 2009).

Comorbid Factors

There are several comorbid factors linked to schizophrenia. Several psychiatric and other disorders are expressed throughout the different phases of schizophrenia. For example, type 2 diabetes, several autoimmune disorders, and cardiac dysregulation have been found to be comorbid with schizophrenia (Ferentinos & Dikeos, 2012). Depression, social phobia, obsessive compulsive disorder, post-traumatic stress disorder, and anxiety symptoms are also among psychiatric comorbidities (Devylder, et al., 2012; Goodwin, et al., 2003; Ciaparelli, et al., 2007). Another comorbid factor is substance abuse. Schizophrenic patients have been found to have a higher rate of substance abuse and increased psychotic effects from the substance abuse (Zeidler, Slawik, Fleischmann, & Greiner, 2012; Brown, et al., 2012; Green, 2006). Interestingly, risk on cancer in schizophrenia patients has been found to be decreased in some studies (Tandon, Nasrallah, & Keshavan, 2009; Catts, Catts, O'Toole , & Frost, 2008; Hippisley-Cox, Vinogradova, Coupland, & Parker, 2007; Barak, Achiron, Mandel, Mirecki, & Aizenberg, 2005).

Heritability

Schizophrenia has a heritability of 80% - 85% (McGuffin, Farmer, Gottesman, Murray, & Reveley, 1984; Shields & Gottesman, 1972; Cardano & Gottesman, 2000; Cardano, et al., 1999). The lifetime risk is 1% but 10 times higher in first degree relatives (Norton, Williams, & Owen , 2006). Recently the focus of heritability studies shifted to specific genes, loci and single nucleotide polymorphisms (SNPs) (Hamshere, et al., 2012). In addition, heritability of specific symptoms and phenotypes are examined (Hamshere, et al., 2011; Chen, Rice, Thompson, Barch, & Csernansky, 2009).

In summary, schizophrenia is a disorder with high heritability and with a great impact on the life of a patient. Not only does it severely reduce the social functioning of patients but also contribute to poor quality of life. The positive and negative symptoms combined with the cognitive deficits reduce the ability of patients to obtain a certain level of independency in life. In addition, schizophrenia also has a severe impact on relatives of the patient. To gain a better understanding of schizophrenia it is interesting to examine some of the underlying mechanisms and changes in neuroanatomy.

Neuroanatomy

One of the first discovered neuroanatomical features in schizophrenia, from post-mortem brain research on deceased schizophrenic patients, is a reduction of brain volume especially cortical volume (Moriguchi, 1981). Advances in imaging techniques made it possible to gain a better understanding of neuroanatomical changes in schizophrenia patients. Data from MRI studies contributed to a better understanding of this reduction in volume. This data showed that there was a reduction in gray matter volume, an increase in ventricular volume and a decrease in whole brain volume (Harvey, et al., 1995; Rimol, et al., 2012; Shenton, Dickey, Frumin, & McCarley, 2001; Steen, Mull, McClure, Hamer, & Lieberman, 2006; Kong, et al., 2012). Reductions were found in the frontal and temporal lobe, more specifically, in the prefrontal cortex, hippocampus, amygdala, superior temporal gyri, corpus callosum, insula, thalamus, the pars triangularis and anterior cingulate (Fig. 2) (Venkatasubramanian, Jayakumar, Gangadhar, & Keshavan, 2008; Mahon, et al., 2012; Sheperd, Laurens, Matheson, Carr, & Green, 2012; Iwashiro, et al., 2012; Palaniyappan, Balain, & Liddle, 2012). The gray matter reduction in the anterior cingulate, medial and inferior frontal lobe and temporal lobe, hippocampus, amygdala, thalamus and insula are common in schizophrenia patients and can enlarge over time. Other changes in brain morphology are dependent on the phase the patient is in and medication (Sheperd, Laurens, Matheson, Carr, & Green, 2012). Some of these reductions in gray matter volume are linked to particular symptoms. Hippocampal abnormalities in anatomy, for example, have been linked to positive symptoms of schizophrenia (Kühn, et al., 2012). Also linked to positive symptoms is reduced volume of the superior temporal gyrus (Sun, Maller, Guo, & Fitzgerald, 2009). Furthermore, reduction in volume of the pars triangularis was correlated with the severity of positive symptoms (Iwashiro, et al., 2012). Thalamus volume has also been correlated to positive symptoms (Rao, Kalmady, Arasappa, & Venkatasubramanian, 2010). Reduction in gray matter volume of the right ventro-lateral prefrontal cortex has been found to correlate with reduced self-reflectiveness (Orfei, Piras, Macci, Caltagirone, & Spalletta, 2012). Insight symptoms were found

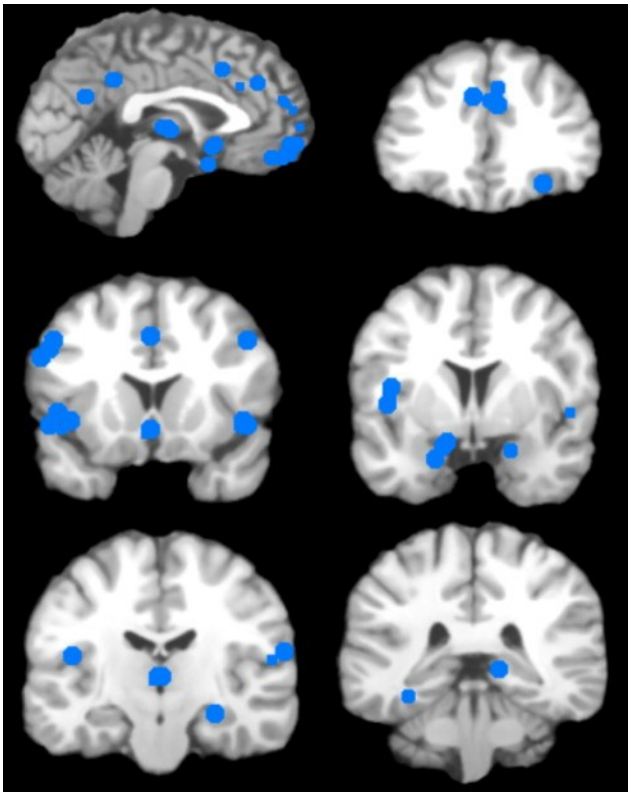

Fig. 2: Areas of the brain with reduced gray matter in schizophrenia compared to healthy controls (Sheperd, Laurens, Matheson, Carr, & Green, 2012)

to correlate with reductions in gray matter volume in the cerebellum, inferior temporal gyrus, medial superior frontal gyrus, and inferior frontal gyrus. Negative symptoms were found to correlate with reductions in gray matter volume of the cerebellum and frontal inferior regions (Bergé, et al., 2011). Most studies found that less volume was correlated to more severe symptoms. Several other studies can be found in literature linking changes in gray matter volume to certain symptoms of schizophrenia, however, it is beyond the focus of this report to cover them all.

Another remarkable change in neuroanatomy in schizophrenia is a disruption of normal cerebral asymmetry, ranging from reduced asymmetry to reversed asymmetry (Pearlson & Murray, 1999; Flaum, et al., 1995). It is assumed that this contributes to the high level of schizophrenia patients which have been found to be ambidextrous (Preti, Sardu, & Piga, 2007; Dragovic & Hammond, 2005). In addition, the disrupted asymmetry contributes to language deficits from which schizophrenia patients often suffer (Li, et al., 2012).

Some of the changes in neurobiology, found in patients with schizophrenia, are not directly induced by schizophrenia. These changes can be induced by external factors closely related to schizophrenia such as antipsychotic medication and substance abuse. Patients treated with haloperidol for example have been found to have a larger reduction in gray matter volume than patients treated with olanzapine. However, it was unclear whether these differences are caused by differences in neurotoxicity of the substances or differences in therapeutic effects (Lieberman, et al., 2005). Nevertheless, chronic treatment with haloperidol and olanzapine have been found to cause an significant, around 20% shrinkage in specific brain regions in macaque monkeys (Dorph-Petersen, et al., 2005). Moreover, antipsychotics blocking the dopamine type 2 receptors (typical antipsychotics), seem to mainly affect the basal ganglia. In patients treated with typical antipsychotics, enlargement of the putamen, and reductions of cortical areas were found. Atypical psychotics, which mainly target the 5-HT2A serotonin receptor, were associated with enlargement of the thalami in treated patients compared to matched untreated patients (Dazzan, et al., 2005). Some of the symptoms of schizophrenia also contribute to the progressions in gray matter volume reduction. Longer periods of untreated psychosis, for example, has been associated with temporal gray matter reduction (Lappin, et al., 2006). Correlation of gray matter reductions with substance abuse are less clear. One study only found a significant correlation in changes in lateral ventricle volume and cerebellar volume (Ho, Andreasen, Ziebell, Pierson, & Magnotta, 2011). However, other studies found significant reductions in gray matter volume in cannabis using schizophrenia patients (Rais, et al., 2008; Bangalore, et al., 2008). The effects of cannabis on brain structure in healthy subjects, is also subject of discussion. One study, for example found clear structural changes in cannabis users whereas another study didn't find any changes at all (DeLisi, et al., 2006; Block, et al., 2000). These differences could be

explained due to differences in amount of cannabis use, MRI scanner field strength, and other factors. However, whether or not cannabis has an effect on neuroanatomy, in schizophrenia patients it might affect neuroanatomy via amplification of some of the symptoms. For example, psychosis can be facilitated by cannabis use (Moore, et al., 2007). And as discussed earlier, psychosis might also contribute to reductions in gray matter volume. Thus, cannabis might be reducing gray matter volume in schizophrenia patients in an indirect manner too.

Together all these changes in neuroanatomy indicate that some of the triggers for schizophrenia are found during cortical development. The next section will cover some genes and pathways which are important during cortical development. In addition, their contribution or possible relation to schizophrenia will be discussed.

Genetic pathways involved in Schizophrenia

Schizophrenia has a high heritability factor of around 80% (McGuffin, Farmer, Gottesman, Murray, & Reveley, 1984; Shields & Gottesman, 1972; Cardano & Gottesman, 2000; Cardano, et al., 1999). Therefore, there must be genetic factors which are specific for schizophrenia. Several genetic studies have been conducted to examine and find genes which are involved in schizophrenia. Thus far, this has been challenging and evidence from different studies is sometimes contradictive or hard to replicate. Furthermore, some of the results seem to be dependent on the population they were sampled in. Genetic studies have identified several chromosomal regions which are correlated to increased risks on schizophrenia. These regions include 1q, 6p, 8p, 13q, and 22q and others (Fanous, 2010; Craddock, O'Donovan, & Owen, 2005; Badner & Gershon, 2002; Lewis, et al., 2003). More recent genome wide association studies, identified SNPs in 1q21.1, 1q24.2, 8p12, 11p11.2, 15q13.3, 16p11.2, and 22q11.2 with schizophrenia (Levinson, et al., 2012; Shi, et al., 2011; Wei-Hua, et al., 2011). Within these regions several candidate genes were identified. Some of these candidate genes and their role in schizophrenia will be discussed. The focus will be on disrupted in schizophrenia 1 (DISC1) since this is one of the first genes discovered to be related to schizophrenia (Millar, et al., 2000). The other genes were chosen based on their interaction with DISC1 and because of their role in cortical development.

DISC1

One of the first discovered candidate genes discovered was disrupted in schizophrenia 1 (DISC1). This gene was discovered in the study of a Scottish family with a history of psychiatric disorders (Fig. 3). Most family members had a (1;11)(q42:q14.3) translocation (Millar, et al., , 2000; Blackwood, et al., 2001). The DISC1 gene is located on 1q 42. 1 (Millar, et al., 2005). It's 13 exons and more than 200kb code for 854 amino acids (The Universal Protein Resource (UniProt), 2012; The Ensembl Project, 2012). The locus in which the DISC1 gene is

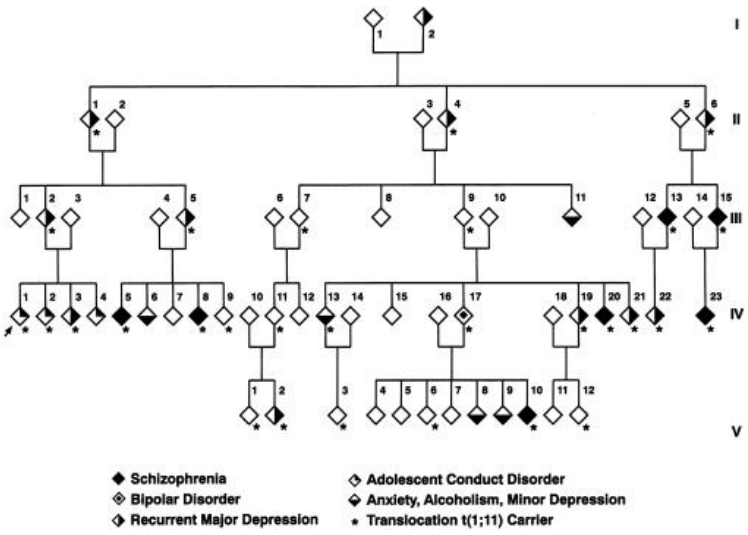

Fig. 3: Family tree of a part of the Scottish family with a (1;11)(q42;q14.3) translocation in which the DISC1 gene was first associated with schizophrenia (Blackwood, et al., 2001)

located is linked to schizophrenia in multiple studies (Ekelund, et al., 2001; Ekelund , et al., 2004). DISC1 is also associated with other disorders, such as, autism and bipolar disease (Hodgkinson , et al., 2004; Kilpinen, et al., 2008). Further linkage of DISC1 to schizophrenia was provided by a study by Callicott *et al.* who examined 12 single-nucleotide polymorphisms (SNPs) in the DISC1 gene. They found strong correlations with schizophrenia for some of the SNPs ([hCV219779 (C)-rs821597 (G)-rs821616 (A)] and (Ser704Cys) in their sample population (Callicott, et al., 2005). So far, genome-wide association studies did not find strong correlations for DISC1 and schizophrenia. This could be caused by an increase in heterogeneity when analyzing larger sample sizes, especially since different SNPs within DISC1 have to been found to have different effects (Hennah, et al., 2009). DISC1 is also correlated to other related psychiatric disorders such as bipolar disease and major depression (Fig. 4) (Millar, James, Brandon, & Thomson, 2004). In addition DISC1 is related to multiple symptoms central in schizophrenia such as social anhedonia, cortical thickness reduction, memory, executive and cognitive processing, and depression (Tomppo, et al., 2009; Braun, et al., 2011; Carless, et al., 2011).

Diagnosis	Number affected	LOD score
Schizophrenia (SCZ)	7	SCZ only, 3.6
Bipolar affective disorder (BP)	1	
Recurrent major depression (MD)	10	SCZ + BP + MD, 7.1
Adolescent conduct disorder	2	
Anxiety, alcoholism, minor depression	1	
Unaffected	8	

Fig. 4: LOD (logarithm of the odds) score of DISC1. The LOD score almost doubles when related psychiatric disorders were included, such as, bipolar disease, and major depression. (Millar, James, Brandon, & Thomson, 2004)

DISC1 has an important role in cortical development both in the pre- and post-natal phase. In rodents, the homolog gene Disc1 has a peak in expression in the late embryonic stages during development of the cortex (Ozeki, et al., 2003). During this period DISC1 is mainly involved in progenitor cell proliferation, radial migration, and neuronite outgrowth and aborization (Shen, et al., 2008; Kamiya, et al., 2005; Ozeki, et al., 2003). Although there is little evidence to support it, there are indications that DISC1 is involved in the maturation and pruning of synapses in the post-natal phase. In addition, DISC1 might be involved in the development of oligodendrocytes and myelination of axons (Camargo, et al., 2007; Roy, et al., 2007). Finally, during adulthood, DISC1 is crucial for neurogenesis in the hippocampus and an important part for cAMP signaling (Shen, et al., 2008; Duan, et al., 2007; Millar , et al., 2000).

Disc1 is a part of the dynein motor complex of rodent PC12 neural precursor cells. Mutated Disc1 was able to interfere with the binding of the Disc1-dynein complex to the centrosome and by interacting with intact Disc1. This mutated Disc1 impaired development of the cortex in rodents. If the same in

humans this might explain some of the disruptions of cortical development in schizophrenia (Kamiya, et al., 2005). DISC1 also interacts with different proteins to be able to exert the previously described role in cortical development. One of these proteins is NDEL1, which is related to LIS1. NDEL1 is involved in cortical development like DISC1. Interaction between DISC1 and NDEL1 has been discovered in a yeast 2-hybrid analysis of the human brain (Ozeki, et al., 2003). DISC1 also interacts with NDE1, which is a homolog of NDEL1, probably in a competitive way (Burdick, et al., 2008). In addition to NDEL1, DISC1 also interacts with other proteins of the centrosome and cytoskeleton, such as, MIPT3 and MAP1A. These proteins are involved in the transportation and localization of receptors to the membrane. Receptors which are transported by these proteins are ATF4, ATF5, ACTN2 and SPTBN4 (Morris, Kandpal, Ma, & Austin, 2003). ATF4 and ATF 5 are activating transcription factors, which bind cAMP inducible promoters (OMIM, 2012; OMIM, 2010). ACTN2 is an actin binding protein and involved in junctions (OMIM, 2008). SPTBN4 is an actin crosslinking protein which links the cell membrane to the cytoskeleton (OMIM, 2001). When truncated, DISC1 fails to interact with these proteins, hereby reducing neuronal migration, outgrowth of axons and dendrites and intracellular transportation (Morris, Kandpal, Ma, & Austin, 2003). Mutated DISC1 also reduced outgrowth of axons and dendrites in rat pheochromocytoma cells (Ozeki, et al., 2003).

Disc1 inhibition of GSK3β in rodents is required for development during the pre-natal phase and in the dentate gyrus in adult animals. If knocked down in the dentate gyrus of adult animals, the animals showed hyperactivity and depression-like symptoms. Inhibition of GSK3β reduced these symptoms. Inhibition of GSK3β is necessary to stabilize CTNNB1, which is crucial for the forming of adherence junctions. Modulation of this protein will modulate neural progenitor proliferation. Mutations in Disc1 can lead to unstable CTNNB1 and thereby disrupt cortical development (OMIM, 2012; Mao, et al., 2009). Phosphorylation of DISC1 also affect proliferation of progenitor cell via GSK3β but via a different pathway (Ishizuka, et al., 2011).

DISC1 also interacts with other proteins such as PDE4B, which is a cyclic nucleotide phodphodiesterase. Phososphodiesterases play an important role in signal transduction by regulation of intracellular levels of cAMP by inactivation (OMIM, 2010). DISC1 regulates PDE4B by binding to it. Hence, mutations in DISC1 can lead to impaired binding to PDE4B, which in turn disrupts cAMP regulation, which is associated to impaired learning and memory and mood disorders (Millar, et al., 2005).

In rodents, Disc1 was found to interact with girdin which is necessary for the migration of neurons of the dentate gyrus. Therefore, Disc1 knockdown caused disruption in the development of the dentate gyrus (Enomoto, et al., 2009). Disc1 knockdown also affected migration of hippocampal neurons in

rodents via increased activation of the Akt signaling pathway. Disc1 affects Akt signaling by inactivation of Kiaa1212, an activator of the Akt pathway (Kim, et al., 2009).

In summary, DISC1, which is an identified risk gene for schizophrenia and other psychiatric disorders, affects cortical development in multiple ways. It binds multiple other proteins and thereby activates and inhibits different pathways. The so far covered targets of DISC1 are just a few examples. The large variety of proteins binding DISC1 might contribute to the fact that there is little evidence from genome wide association studies linking DISC1 to schizophrenia. However, since it is strongly related schizophrenia in particular cases and because it is involved is several mechanisms driving schizophrenia, it seems an interesting target for further research. This research can be directed to proteins and genes interacting with DISC1. In addition to the earlier discussed GSK3β and NDEL1, recent evidence suggests that DISC1 also interacts with other targets which are crucial for cortical development. These targets include DIXDC1, PCM1, BBS4, APP, and LIS1 (Kamiya, Sedlak, & Pletnikov, 2012; Kamiya, et al., 2005; Burdick, et al., 2008; Kamiya, et al., 2008; Singh, et al., 2010; Namba & Kaibuchi, 2010; Bradshaw & Porteous, 2012). In the next section these targets and their relation with DISC1 will be examined to gain a better understanding of their role in cortical development and schizophrenia.

GSK3β

Glycogen synthase kinase 3-beta, or GSK3β, is a protein-serine kinase which is involved in differentiation and development of neurons, metabolism and formation of body pattern (Stambolic & Woodgett, 1994). The first evidence that GSK3β might be involved in schizophrenia came from the discovery that inhibition of GSK3β had the same effect as lithium in Xenopus (Klein & Melton, 1996). Lithium is a potent drug for the treatment psychiatric diseases, such as, bipolar disorder, major depression and certain forms of psychosis.

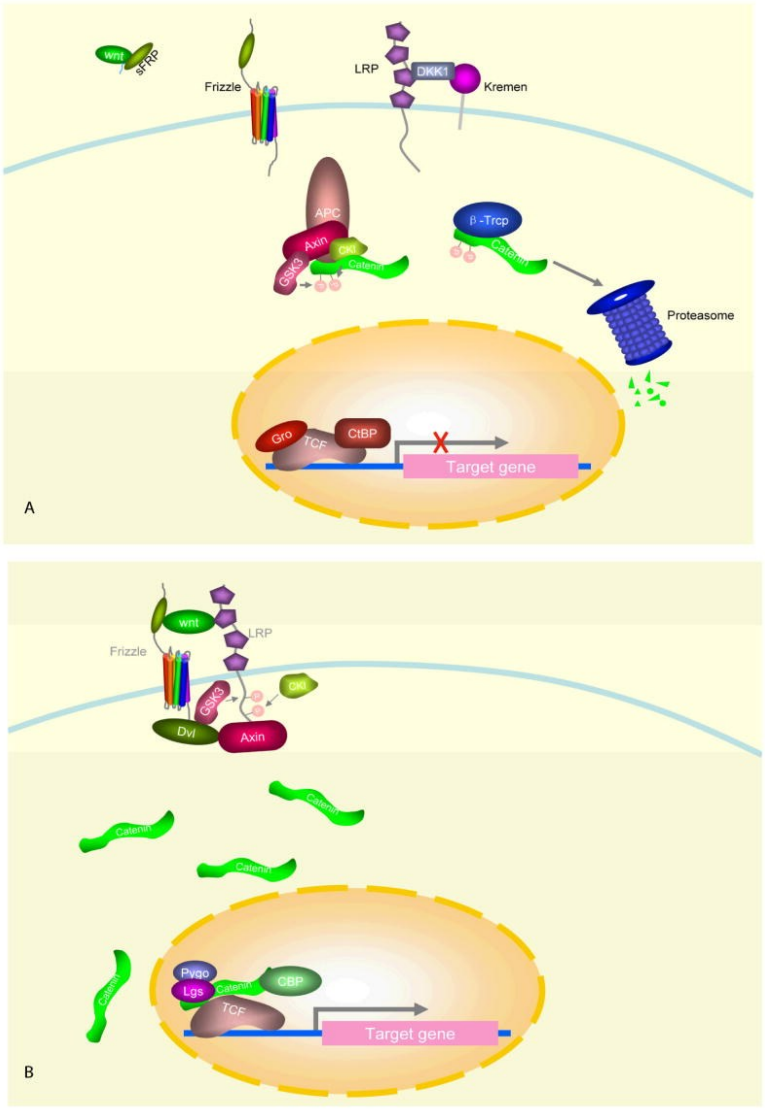

Fig. 5: GSK3β in the Wnt pathway. When active GSK3β ubiqitinates catenin which is then degraded in the proteasome (a). When the Wnt pathway is activated or GSK3β is inhibited, catenin is not degraged and activates gene transcription in the nucleus (b). (Chen, Yang, Evans, & Liu, 2008)

GSK3β in involved in several pathways. One of the most important pathways for schizophrenia is the Wnt pathway (Fig. 5). GSK3β and its homolog GSK3α are part of a protein complex that ubiquitinates several proteins, including β-catenin (MacDonald, Tamai, & He, 2009). β-catenin is part of the Wnt pathway and an activator of genes which trigger progenitor proliferation which is crucial for proper cortical development (Mao, et al., 2009). In addition, the Wnt signaling pathway is able to inhibit the GSK3 complex activity via separation of the enzyme of its substrates (Taelman, et al., 2010; Stambolic, Ruel, & Woodgett, 1996). In humans, β-catenin has been found to be reduced in several hippocampal areas (Cotter, et al., 1998). In addition, mutation of a receptor in the Wnt pathway (FZD3) is also associated with schizophrenia (Katsu, et al., 2003). Finally, there is evidence that increases in GSK3β gene copy number variation are associated with bipolar disorder and probably other psychiatric disorders (Lachman, et al., 2007). Moreover, genetic inactivation of

GSK3α produced normalized behavioral effects in Disc1 mutant mice (Lee, Kaidanovich-Beilin, Roder, Woodgett, & Wong, 2011). This evidence shows that defects in the Wnt pathway can play a role in schizophrenia.

Other pathways which are dysregulated by GSK3 are the Notch and sonic hedgehog (Shh) pathways, which are important for neural progenitor development and differentiation. In this study, GSK3 deletion caused hyperprofilation of neural progenitors in mice. In addition, an increase in Notch signaling was detected. The increase in Notch signaling seemed to be linked to GSK3β, but independent of Wnt signaling. The GSK3 knockout also induced an increase in Shh signaling (Kim, et al., 2009). Based on these results, GSK3 seems to have an inhibiting effect on the Shh and Notch signaling pathways. Mutations in some of the Notch genes have been associated with increased risks on schizophrenia (Gregorio, et al., 2006; Ujike, et al., 2001; Prasad, et al., 2004). No evidence linking Shh signaling directly to schizophrenia has been published yet, but there are some implications. For example, Shh signaling seems to be crucial for dopaminergic progenitor pools in the midbrain. Defects in these neurons are an underlying mechanism for schizophrenia. Expression of Shh in the early dopaminergic progenitors is crucial for proper development of the midbrain dopamine neurons (Joksimovic, et al., 2009).

Altogether, GSK3β can play a role in the development of schizophrenia via multiple pathways and interactions. As discussed briefly earlier, DISC1 has an inhibitory effect on GSK3β. Hence, mutations in DISC1 can affect GSK3β activity and thus cortical development, via the formerly described pathways.

DIXDC1

Another interesting factor in schizophrenia might be DIX Domain-Containing Protein 1 (DIXDC1) because it interacts with DISC1 to modulate GSK3β activity (Mao, et al., 2009). The DIXDC1 gene is 45kb long and contains 16 exons. It is located on chromosome 11q23.1 (Katoh & Katoh, 2003). During embryonic proliferation of neural progenitors DISC1 is regulated via interaction with DIXDC1. Binding with DIXDC1 is required for the inhibition of GSK3β, which subsequently inhibits degradation of β-catenin. During migration of neurons DIXDC1 affects interaction of DISC1 via NDEL1. This will be covered in more detail in the next section (Fig. 6) (Singh, et al., 2010). As discussed earlier, evidence suggests an important role for GSK3β and DISC1 in schizophrenia. The interaction with DIXDC1 might play a central part in the development of schizophrenia in specific patients. To support this hypothesis, a recent study showed that Dixdc1 knockout mice displayed decreased spontaneous locomotor activity, abnormal behavior in an elevated plus maze, and impaired startle behavior. These changes in behavior are comparable to other mouse model of schizophrenia (Kivimäe, et al., 2011). In addition, in a convergent functional genetics study, DIXDC1 popped up as candidate gene for schizophrenia out of genome wide association study data (Ayalew, et al., 2012). DIXDC1 also interacts with NDEL1 which also interacts with DISC1. The next section will focus on NDEL1 to examine if it is relevant in schizophrenia.

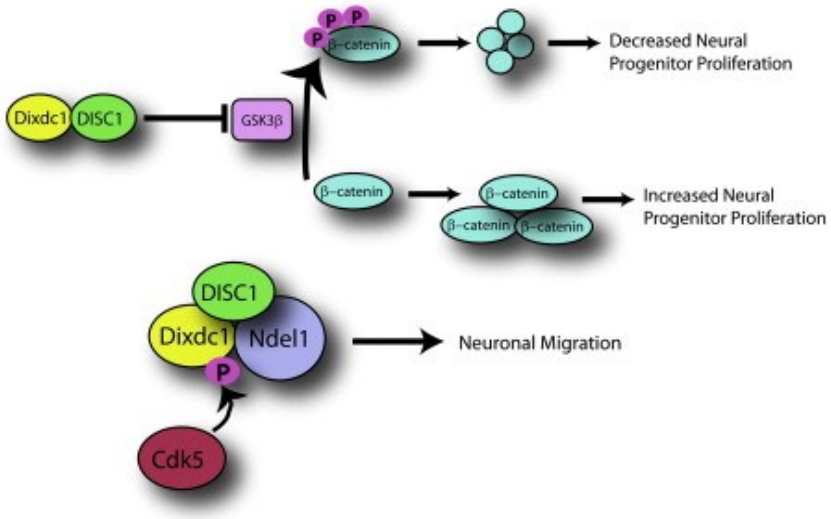

Fig. 6: Proposed DIXDC1 functioning. Binding of DIXDC1 to DISC1 is required to exert its inhibitory effects on GSK3β. When GSK3β is inhibited, β-catenin will not be degraded and neural progenitor proliferation will be increased. In addition, DIXDC1 is able to stimulate neural migration by additional interaction with NDEL1. (Singh, et al., 2010)

NDEL1 and LIS1

Nuclear Distribution nudE-Like 1 (NDEL1 or NUDEL) interacts with DISC1 and plays a role in cortical development (Ozeki, et al., 2003). The NDEL1 gene is located on 17p13.1. (OMIM, 2010). NDEL1 regulates microtubule dynamics and is therefore crucial for cell division and neuronal migration (Sasaki, et al., 2005). Failure of the binding of DISC1 to NDEL1 reduced neurite outgrowth in PC12 cells (Ozeki, et al., 2003). DISC1 binding to NDEL1 is crucial for stabilization of the dynein motor complex (Kamiya, et al., 2005). One proposed way in which NDEL1 could be involved in schizophrenia is via its relationship with NDE1 (a homologue of NDEL1). Both NDE1 and NDEL1 can bind DISC1. NDEL1 binds stronger to DISC1 when there is a cysteine at position 704 whereas NDE1 binds stronger to a serine at that position. This suggest competitive binding of NDE1 and NDEL1 to DISC1. Mutations in DISC1 might change the NDE1/NDEL1 binding ratios and disrupt neuronal migration (Burdick, et al., 2008). Furthermore, expression of NDEL1 was significantly decreased in hippocampal and dorsolateral prefrontal cortex tissue from schizophrenia patients. This decrease was associated with mutation in the DISC1 gene (Lipska, et al., 2006). Additionally, NDEL1 is able to bind the same region of DIXDC1 as DISC1. Phosphorylation of DIXDC1 by CDK5 is crucial for this interaction. Both the binding of DISC1 and NDEL1 are needed for neuronal migration (Singh, et al., 2010).

NDEL1 interacts with Platelet-Activating Factor Acetylhydrolase Isoform 1B (PAFAH1B1 or Lissencephaly 1 (LIS1)) too (Yan, et al., 2003). Together with 14-3-3epsilon they form a complex. In this complex, 14-3-3 is responsible for the correct localization of NDEL1 and LIS1 along axons (Fig. 6). DISC1 interacts with this complex via Kinesin-1. DISC1 lacking the capacity to bind the LIS1/NDEL1 complex caused a reduction in axonal growth. The same happened with altered versions of LIS1 or NDEL1 (Taya, et al., 2007). In addition, LIS1 interacts with dynein which is important for transportation along microtubule and for positioning of the centrosome during migration (Fig. 7). Decreased Lis1 expression in mice caused a change in dynein distribution with a decrease of 50% in perinuclear dynein (Smith, et al., 2000). Mutations in LIS1 usually lead to lissencephaly. Lissencephaly severely impacts cognitive functioning and life expectancy. Hence, it could be to examine the role of LIS1 in

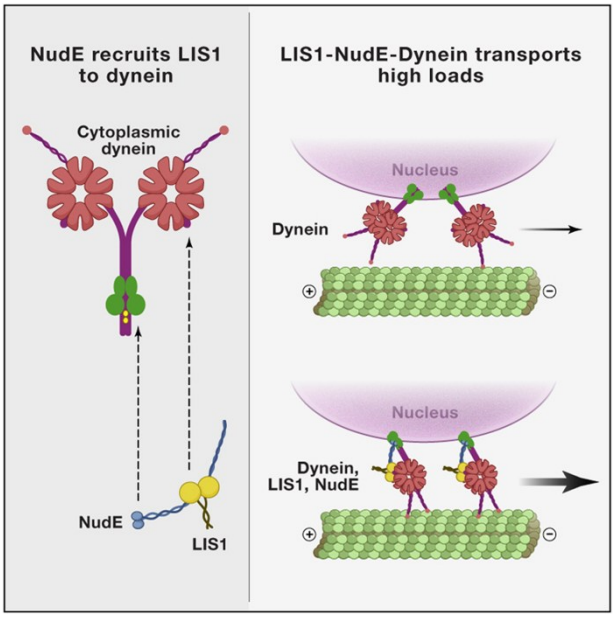

Fig. 7: NDEL1 (NudE) binds LIS1. Next both bind dynein. Next, the NDEL1/LIS1 complex secure attachment to the microtubules when dynein is transporting load. (McKenney, Vershinin, Kunwar, Vallee, & Gross, 2010)

schizophrenia. Nevertheless, reduced levels of LIS1 mRNA have been found in hippocampal and dorsolateral prefrontal cortex tissue of schizophrenia patients (Lipska, et al., 2006). There are also other pathway that are involved in neuronal migration and interact with DISC1. One of those is the PCM1-BBS4 mediated pathway. This pathway will be examined in the next section

PCM1 and BBS4

Pericentriolar Material 1 (PCM1) is located on 8p22 (Corvi, Berger, Balczon, & Romeo, 2000). PCM1 is essential for cell division, which was discovered because PCM1 antibodies, PCM1 deletion and PCM1 interference with siRNA all cause a cell-cycle arrest. PCM1 is involved in interactions between microtubule and the centrosome (Dammermann & Merdes, 2002). Its association with schizophrenia is subject of debate. One study found that clozapine, a very efficient drug in the treatment of several psychiatric disorders including schizophrenia, changed the expression of PCM1 (Rizig, et al., 2012). In addition, several studies found evidence that certain SNPs in PCM1 were linked to schizophrenia (Moens, et al., 2010; Gurling, et al., 2006; Datta, et al., 2010). However, a recent study found no significant associations between SNPs or different PCM1 haplotypes and schizophrenia (Hashimoto, et al., 2011). However this study was based on data from a Japanese population, whereas the other studies were based on data from Caucasian populations.

DISC1 interacts with PCM1. A Ser704Cys mutation and Leu607Phe mutation in DISC1 both affected the distribution of PCM1 in the cell (Eastwood, Walker, Hyde, Kleinmann, & Harrison, 2010; Eastwood, Hodgkinson, & Harrison, 2009). Interestingly, a mutation at 704 also affected NDEL1/NDE1 affinity for DISC1 as discussed earlier. PCM1 forms a complex with DISC1 and Bardet-Biedl syndrome 4 (BBS4), which are both required for the guidance of PCM1 to the centrosome. Inhibition of PCM1 or DISC1 causes disruptions in neuronal migration (Kamiya, et al., 2008). This data shows that PCM1 has a role in schizophrenia albeit possibly population specific. How about BBS4?

BBS4 is located on 15q24.1 and is identified as a cause for the Bardet-Biedl syndrome. This syndrome is an inherited disorder with several psychiatric symptoms. Other symptoms involve, obesity, renal dysfunction and polydactyly. BBS4 is localized pericentrosomally and is involved in intracellular transport along microtubule and anchoring of the microtubule. In addition it is necessary for cell division (Kamiya, et al., 2008; Kim, et al., 2004). BBS4 inhibition caused neuronal migration defects due to disrupted neuronal migration (Kamiya, et al., 2008). Unfortunately there is no evidence from population studies to confirm that BBS4 is indeed a risk factor for schizophrenia yet.

APP

The gene coding for Amyloid Precursor Protein (APP) is located on 21q21.3 and has 18 exons (Blanquet, et al., 1987). APP is commonly associated with Alzheimer's disease because amyloid plaques, found in Alzheimer's disease patients, are composed of beta amyloid (Walsh & Teplow, 2012). However, this gene is also interesting in the context of schizophrenia since recent data shows that there is an interaction between APP and DISC1 which is crucial for the regulation of migration of cortical precursor cells (Young-Pearse, Suth, Luth, Sawa, & Selkoe, 2010). This section will cover the functions of APP in cortical development and then focus on its relevance for schizophrenia.

APP is modified after translation in several way, including, phosphorylation, glycosylation, and tyrosine sulfatation as well as cleavage by alpha-, beta-, and gamma-secretases (De Strooper & Annaert, 2000; Sennvik, et al., 2000). This cleavage takes place extracellularly by the membrane bound beta-secretase. Next, cleavage by the gamma-secretase creates the intra and extra cellular domains of APP (Yan, et al., 1999; Pardossi-Piquard, et al., 2005). APP interacts with Death Receptor-6 (DR6) which causes cell body death and axonal pruning, which are important for cortical development (Nikolaev, McLaughlin, O'Leary, & Tessier-Lavigne, 2009). Although theoretically this process might be involved in schizophrenia, no data supporting this theory can be found in literature. However, APP also interacts with DISC1 and the previously covered NDEL1/LIS1 complex. More specifically, the intracellular domain of APP binds to the N-terminal of DISC1. This interaction happens downstream of APP. Knockdown of APP in cultured neurons caused a change in DISC1 distribution. And overexpression of DISC1 was able to compensate for the loss of APP (Fig. 8).

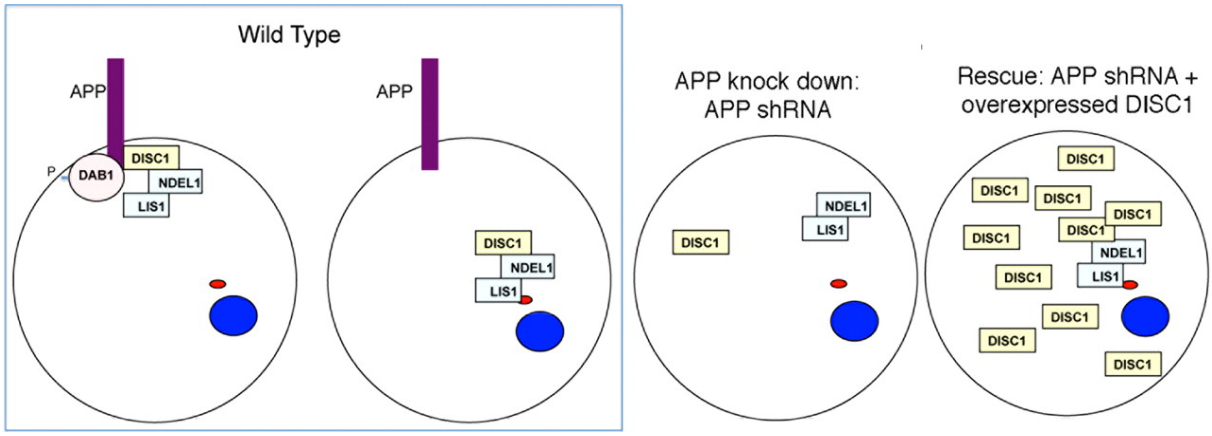

Fig. 8: The intracellular domain domain of APP interacts with DISC1, presumably to translocate it towards the centrosome. APP knockdown caused a dysfunctioning of DISC1-NDEL1-LIS1 activity and distribution. Overexpression of DISC1 compensated for the APP knockdown. (Young-Pearse, Suth, Luth, Sawa, & Selkoe, 2010)

Presumably the APP-DISC1 interaction facilitates the distribution of DISC1 towards the centrosome. As discussed earlier, the DISC1-LIS1-NDEL1 complexes play a pivotal role in neuronal migration via their interaction with the centrosome and microtubuli (Young-Pearse, Suth, Luth, Sawa, & Selkoe,

2010). Based on this evidence, mutations in APP will affect DISC1 mediated cell migration in theory. The discovery of a mutation in codon 713 of the APP gene in a schizophrenic patient provided the first evidence to prove this theory (Jones, et al., 1992). However, this mutation has only been found in one patient. And a more recent study concluded that mutations in APP are unlikely to cause schizophrenia (Asherson, et al., 2005). Still the relationship between APP and schizophrenia might lie in other factors, such as, mutations in the secretases. Savonnenko *et al.* found that a beta-site APP cleaving enzyme 1 (BACE1) knockout mice showed signs which are associated with rodent models of schizophrenia. These signs included, pre-pulse inhibition, novelty-induced hyperactivity, hypersensitivity to a glutamatergic psychostimulant (MK-801), cognitive impairments, and deficits in social recognition. Moreover, treatment with clozapine reduced some of these symptoms, contributing to its validity (Savonenko, et al., 2008). However, studies in human populations have to prove that mutations in these genes are truly a risk factor in schizophrenia.

Discussion

Schizophrenia is a mental disorder with a broad spectrum of symptoms. Although severity of the disorder can differ between patients, it always has a severe impact on quality of life of the patient. Characteristics for schizophrenia are changes in neuroanatomy. These changes indicate abnormal cortical development, triggered by internal or external factors. Because of the high heritability of schizophrenia, it is likely that some of these changes are driven by genetic factors. Several SNPs in genes have been associated to certain forms of schizophrenia in certain populations. One of them is DISC1.

There is growing evidence linking DISC1 mutations to schizophrenia and other psychiatric disorders such as autism and bipolar disorder. DISC1 is involved in neuronal migration, neural progenitor proliferation and neurogenesis both in the pre- and post-natal phase. Hence, mutations which functionally alter DISC1 can lead to disruptions in cortical development. To exert its effect DISC1 interacts with multiple other genes, proteins, and pathways. So far, certain SNPs in DISC1 have been associated with schizophrenia. However, no genome wide association study has found strong correlations for these SNPs or DISC1 with schizophrenia. This might be explained via the multiple interactions and roles DISC1 has in cortical development. Hence, different DISC1 related dysfunctions can contribute to schizophrenia. In large population studies like genome wide association studies multiple DISC1 related correlation might be found which are too weak to be detected. Maybe, if grouped together all DISC1 related issues might produce a much stronger correlation with schizophrenia. In addition, other studies in smaller populations and animal studies show that disruption of DISC1 is related to schizophrenia or produces similar symptoms. Therefore, DISC1 remains an interesting target for schizophrenia research. However the focus of the research might have to shift more to interaction of DISC1 with other factors.

Some of the factors with which DISC1 interacts and which are involved in cortical development were covered in this report. One of them is GSK3β, which has been found to interact with DISC1. More specifically, DISC1 has an inhibitory effect on GSK3β which is similar to the effects of lithium. GSK3β is involved in multiple pathways, including Wnt, Notch, and Sonic Hedgehog. GSK3β has an inhibitory effect on all of these pathways. There is growing evidence linking the Wnt pathway to schizophrenia. In animal models, Notch and Shh were also linked to schizophrenia. Furthermore, mutations in some of the Notch genes were linked to increased risks on the disease. No solid evidence in humans has been found for Shh yet but there are implications that Shh is indeed a risk factor too. Further research focusing on these pathways in humans might help clarifying their role further. Last but not least, GSK3β copy number variations were directly associated with related disorders such autism and bipolar disorder. In conclusion, GSK3β is an interesting target for further investigation.

Recent evidence indicated that DIXDC1 could also be a risk factor for schizophrenia. Since this factor is involved in two different pathways related GSK3β and NDEL1 its role might be complex. So far it is clear that DIXDC1 interacts with DISC1 to exert its effects. Animal studies showed that DIXDC1 knockout produced schizophrenia like behavior. In addition, DIXDC1 was found to be a risk factor in a recent genetics study. The interaction with DIXDC1 is a fine example of the complexity of DISC1 related regulation and how it involves multiple factors which might contribute to schizophrenia.

Another pathway which is modulated by DISC1 is the NDEL1-LIS1 mediated cell division and neuronal migration. Interaction with DISC1 (and DIXDC1) is necessary for the NDEL1-LIS1 complex to bind microtubuli, which in turn is essential for cell division and neuronal migration. Decreases in NDEL1 expression have been found in schizophrenia patients showing that it is can indeed be a risk factor for schizophrenia. Data presenting LIS1 as risk factor of schizophrenia is scarce. Animal studies showed that decreased LIS1 expression produced symptoms which were considered causal for schizophrenia. In humans, reduced levels of LIS1 mRNA have been found in hippocampal tissue of schizophrenia patients. However, linking LIS1 mutation to schizophrenia might be problematic since most LIS1 mutation cause lissencephaly. This is such a severe mental disorder that it might overshadow, or make it hard to diagnose, schizophrenia. In any case, this implies that further research into LIS1-NDEL1 defects in schizophrenia patients might produce useful data.

DISC1 interacts with PCM1 and BBS4 as well. Like the NDEL1-LIS1 complex PCM1-BBS4 is also involved in interactions of the centrosome with microtubuli, important for migration and cell-division. Another similarity is that both systems share a location of interaction with DISC1. Different mutations in the same amino acid position (704) in DISC1 caused differences activity of both the NDEL1-LIS1 system as the PCM1-BBS4 system. This implies that one mutation in DISC1 might in fact affect two different systems and might thereby be more severe than expected. The association of PCM1-BBS4 with schizophrenia is less evident than that of NDEL1-LIS1. PCM1 has been found in specific populations to be related to schizophrenia, but not in others. The data so far suggest that PCM1 is a risk factor in Caucasian populations but not for Japanese populations. Further analysis of this aspect might be very interesting as it can contribute to understanding of differences in schizophrenic genotypes across different populations. In conclusion, evidence suggest a role for PCM1-BBS4 in schizophrenia, and there is still a lot to explore about these factors.

Last but not least, APP has also been found to interact with DISC1. APP is generally related to Alzheimer's disease, which shares some symptoms with schizophrenia. For example, psychosis, impaired cognitive functioning and thinking, depression, anxiety, and impaired memory are found in both disorders. Of course there are a lot of differences too, such as, age of onset. In addition loss of

memory is less severe in schizophrenia compared to Alzheimer's disease. APP affects cortical development in multiple ways, one being via induction of cell-death. Another one is via the LIS1-NDEL1 system which affects neuronal migrations and cell-division, as discussed previously. Not much is known about the role of APP in cell-death in relation to schizophrenia. However since this can affect cortical development, it can be interesting to examine this in a schizophrenia context. APP's interaction with NDEL1-LIS1 is mediated via DISC1 and this pathway has been identified as possible risk factor for schizophrenia. Moreover, a knockdown of APP in rodents caused a change in DISC1 distribution which can be a risk factor for schizophrenia. Human data however, suggest that mutations in APP are not likely to cause schizophrenia. Still APP might be involved in schizophrenia, albeit not directly but indirectly, by mutations in secretases of APP. One of these mutations in rodents produced schizophrenia like symptoms. Hence, involvement of APP might be more complex and contributable to external factors which produce non-functional APP. Focusing research efforts on a better understanding of the role of APP and its secretases might clarify the role of APP but also DISC1 in schizophrenia.

In summary, DISC1 a risk factor on schizophrenia, seems to display multiple ways in which it can contribute to schizophrenia. In this report only a few which were specifically involved in cortical development were examined. However, there are many more factors with which DISC1 interacts. This example of pleiotropic effects of DISC1 nicely illustrates the complexity underlying the development of schizophrenia. In addition, schizophrenia is a very diverse disorder. Since it's classification is not based on underlying mechanisms but on symptoms, finding strong associations with genetic factors might be very hard, especially in genome wide association studies across different populations. A better understanding of some of the underlying mechanisms might contribute to a way to sub-classify different forms of schizophrenia. This can aid to more specific genetic studies which in turn can find stronger associations for more complex risk factors in schizophrenia. For example, based on information discussed in this report, one could think of creating a DISC1 class of schizophrenia. In this class, all DISC1 related forms of schizophrenia can be accumulated. This will make it easier to examine the different sub-factors, such as the ones discussed here. In addition, this can lead to better diagnosis of schizophrenia as genetic screen becomes more available and screening on specific risk factors will be easier. If detected early, severe symptoms of schizophrenia can be therapeutically suppressed. This will lead to a better quality of life for (potential) patients.

Therapeutic targets

This study has covered multiple factors which can contribute to schizophrenia. This last section will examine how this information can be used to look for potential targets for pharmacological intervention.

As mentioned earlier, a commonly used drug in the treatment of several mental disorders is lithium. Lithium was found to inhibit GSK3β. Interestingly, a clinical trial using only lithium to treat patients with schizo-affective disorders found that lithium improved patient's condition. However, this improvement was smaller than treatment with another anti-psychiatric drug, chlorpromazine (Prien, Caffey & Klett, 1972). Another study found the effect of lithium to be as effective as chlorpromazine (Brockington, 1978) Based on these results and the previously discussed data, GSK3β is a valid target for pharmacological intervention especially since it is involved in multiple pathways which are important for progenitor proliferation. When DISC1 mediated inhibition of GSK3β fails, pharmacological inhibition could provide for a way to prevent related disruption in cortical development. One way to interfere with GSK3β is via morpholino-oligonucleotides which has proven successful in inhibition of GSK3β in the rat pancreas (Figeac, Ilias, Bailbe, Portha, & Movassat, 2012). However, modifications in delivery method will be necessary to ensure proper delivery of the morpholino-oligonucleotides in the brain. However, the existence of other isoforms of GSK3β which are non-interchangeable in combination with poor selectivity, cell permeability and stability of current GSK3β inhibitors renders them not very efficient (Meijer, Flajolet, & Greengard, 2004). Alternatives could focus on activation of one of pathways which are inhibited by GSK3β. However, care must be taken since, for example, over activation of the Wnt pathway could lead to cancer (Moon, Kohn, De Ferrari, & Kaykas, 2004). In summary, GSK3β might be a very useful target for the treatment of schizophrenia. However, it might also be very difficult to develop specific drugs.

Contrary to the inhibition of GSK3β, for the other pathways discussed in this paper, stimulation can be helpful in schizophrenia patients. It is very interesting to investigate if dysfunctioning of either the NDEL1-LIS1 pathway or the PCM1-BBS4 can be compensated by stimulation of the other pathway. Especially since these pathways share multiple similarities. In addition, increasing DISC1 expression might also be helpful. Current atypical anti-psychotics are already achieving this (Chiba, et al., 2006). However, further research might be able to produce information which can be used to create pharmacological agents which are more specific. Hence, reducing side effects.

Better understanding of the underlying mechanisms of schizophrenia can lead to more specific diagnosis. In the future, that information can be used to prescribe patients specific medication, which precisely targets the deficits in the patient. In addition, further investigation of effects of DISC1 per

region will contribute to even more specific treatment and identification of schizophrenia. This will hopefully lead to a reduction of the burden of this disease.

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