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Molecular Mechanisms of Schizophrenia

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Abstract
Schizophrenia is a complex disorder, where family, twin and adoption studies have been demonstrating a high heritability of the disease and that this disease is not simply defined by several major genes but rather evolves from addition or potentiation of a specific cluster of genes, which subsequently determines the genetic vulnerability of an individual. Linkage and association studies suggest that a genetic vulnerablility, is not forcefully leading to the disease since triggering factors and environmental influences, i.e. birth complications, drug abuse, urban background or time of birth have been identified. This has lead to the assumption that schizophrenia is not only a genetically defined static disorder but a dynamic process leading to dysregulation of multiple pathways. There are several different hypothesis based on several facets of the disease, some of them due to the relatively well-known mechanisms of therapeutic agents. The most widely considered neurodevelopmental hypothesis of schizophrenia integrates environmental influences and causative genes. The dopamine hypothesis of schizophrenia is based on the fact that all common treatments involve antidopaminergic mechanisms and genes such as DRD2, DRD3, DARPP-32, BDNF or COMT are closely related to dopaminergic system functioning. The glutamatergic hypothesis of schizophrenia lead recently to a first successful mGlu2/3 receptor agonistic drug and is underpinned by significant findings in genes regulating the glutamatergic system (SLC1A6, SLC1A2 GRIN1, GRIN2A, GRIA1, NRG1, ErbB4, DTNBP1, DAAO, G72/30, GRM3). Correspondingly, GABA has been proposed to modulate the pathophysiology of the disease which is represented by the involvement of genes like GABRA1, GABRP, GABRA6 and Reelin. Moreover, several genes implicating immune, signaling and networking deficits have been reported to be involved in the disease, i.e. DISC1, RGS4, PRODH, DGCR6, ZDHHC8, DGCR2, Akt, CREB, IL-1B, IL-1RN, IL-10, IL-1B. However, molecular findings suggest that a complex interplay between receptors, kinases, proteins and hormones is involved in schizophrenia. In a unifying hypothesis, different cascades merge into another that ultimately lead to the development of symptoms adherent to schizophrenic disorders.

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Introduction

Schizophrenia is a severe psychiatric disorder, which is equally prevalent in men and women and affects approximately one percent of the population worldwide. Several factors have been found to be associated with an increased risk to develop schizophrenia. In general, schizophrenia is considered to be a complex disease with multiple factors contributing to the pathogenesis. The cascade of schizophrenia is possibly triggered by several turning points, i.e. "stressors" like infections, birth complications, drug abuse, urban background or time of birth (higher occurrence for winter born individuals possibly due to viral triggers), but the basic risk profile is mainly depending on causative genes, which is underpinned by heritability of schizophrenia with up to 80% in monozygotic twins [1]. Other aspects such as low economic status and divorced or single marital status, which had previously been attributed to a higher risk of schizophrenia are more likely to be a result of the disease and its related negative consequences [2].

The diagnosis according to DSM-IV criteria is based on the concomitant appearance of at least two of the following symptoms each presenting for a significant portion of time during a 6-month period: delusions, hallucinations, disorganized speech (e.g., frequent derailment or incoherence), grossly disorganized or catatonic behaviour and negative symptoms, i.e., affective flattening, alogia, or avolition. Typically symptoms can be separated into positive, negative and cognitive symptoms. Positive symptoms, which can be treated most effectively by the use of antipsychotics include delusions of reference, paranoid delusions, somatic delusions, hallucinations (mostly hearing voices) and catatonic behaviour. Negative symptoms include lack of emotion, the inability to enjoy activities, low energy, lack of interest in life, affective flattening, alogia, inappropriate social skills, inability to make friends, social isolation. Cognitive symptoms that are sometimes classified as part of the negative symptoms are particularly related to attention, working memory, and executive functions. As distinct classes of drugs, dopaminergic agonists (D-amphetamine), serotonergic agonists (LSD), and glutamatergic antagonists (phencyclidine, [PCP]) all induce psychotic states in experimental animal settings and humans, and some of their antagonists are involved in modern effective psychopharmacological treatment strategies.

Several neurotransmitter systems and functional networks within the brain have been found to be affected in patients with schizophrenia. The question is not completely resolved if these alterations are causative for the development of schizophrenia, or if they have to be considered as consequences of disease progression or treatment. The following review will highlight the most important findings in schizophrenia research. Both, recent molecular as well as genetic data will be shown. Genetic analyses in complex diseases encounter several problems that partly explain the sometimes ambiguous results. One strategy to resolve these problems was the introduction of endophenotypes, clinical or functional variables, e.g. functional or structural imaging data or neurophysiological parameters, that are closely related to an underlying complex disorder [3]. Schizophrenia was connected to measurable traits including neurophysiological abnormalities, working memory changes or schizotypal personality traits [4-6]. It is assumed that only a small amount of genetic factors is involved in the formation of a particular endophenotype, which facilitates the detection of single genetic variants. However, since this topic has raised many questions and criticism and requires its own review, we have decided to omit the association of endophenotypes with genetic data for the main part of the present review.

Schizophrenia as a complex genetic disorder

Schizophrenia is a complex disorder, which is not simply defined by several major genes but rather evolves from addition or potentiation of a specific cluster of genes, which subsequently determines the genetic vulnerability of an individual [7, 8]. Therefore, in association studies of single genes the levels of statistical significance are low and estimated effect sizes in these small individual studies are modest. In general, two approaches have been used, linkage and allelic association studies. In linkages studies, large pedigree samples are analyzed to identify chromosomal regions that are likely to harbor genes that are involved in the disorder. Association studies focus on genetic polymorphisms that are supposed to alter the expression or function of a gene that is supposed to be involved in schizophrenia. The selection of candidate genes arises from their known function (functional candidates) or from their chromosomal localization (positional candidates). A large variety of functional and/or positional candidate genes arise from their known function (functional candidates) or from theirs chromosomal localization (positional candidates) and have been evaluated over the past years. Although many positive findings could be de-

tected, many findings could not be replicated in subsequent studies. Small sample size, genetic heterogeneity, recruitment bias, statistical limitations and diverging ethnic populations may explain only some reasons for conflicting results. Also genetic variants such as single nucleotide polymorphisms (SNPs), may often have only minor impact on gene expression and function. Advancement has been achieved through meta-analyses and the evaluation of haplotypes that encompass several neighboring SNPs and also give information on phase determination for each chromosome.

Moreover, the findings deriving from linkage studies often yielded only broad chromosomal regions of interest, which led to conflicting results. There are two meta-analyses of linkage studies that have implicated loci on various chromosomes in schizophrenia and schizoaffective disorder: Lewis et al. found in 1208 families with schizophrenia and schizoaffective disorder and in 2945 affected individuals a high number of loci that meet aggregate criteria for significance 1p, 2q, 2q, 3p, 5q, 6p, 11q, 13q, 14p, 20p, 8p and 22p [9]. Another meta-analysis of Badner and Gershon found 8p, 13q, 22q to be associated with schizophrenia and schizoaffective disorder in 681 families with 1929 individuals being affected [10]. The problem arises, that the strongest linkage finding in the study of Lewis et al. (on chromosome 2) was not detected by Badner and Gershon [9, 10]. Segurado et al. examined 347 families with 1595 individuals being affected and found association with 9p, 10q, 14q, 18q [11]. Another genome wide linkage analysis of Japanese sib-pair samples comprising 236 Japanese families with 268 non-independent individuals with schizophrenia confirmed linkage of schizophrenia to chromosome 1p, 14q and 20p [12]. In a linkage study of DeLisi et al. including schizophrenic and schizoaffective patients, attention was drawn on chromosome 1, 2, 14, and 8, while another large study on schizophrenia and schizoaffective disorder by Suarez et al. pointed to chromosome 5, 8, 10, and 11 [13, 14]. The problem arises, that most of the 24 chromosomes have been linked nowadays to schizophrenia and subsequent meta-analysis occasionally failed in replicating further claimed regions. Another problem is the fact, that several candidate genes are not located in chromosomal regions of interest. It has recently been concluded that most promising findings for schizophrenia were obtained on chromosome 6q, 13q, 18 and 22q and these regions were also implicated in manic depressive illness or bipolar disorder [15], which arises moreover the question of diagnostic specifity.

The neurodevelopmental hypothesis of schizophrenia

The neurodevelopmental hypothesis of schizophrenia postulates that effects during embryonal and fetal brain development lead to defective neural connectivity and altered biochemical functioning resulting in cognitive, emotional and intentional dysfunction later in life [16,17]. The cerebral alterations observed in schizophrenic post-mortem brain that might be related to neurodevelopmental disturbances have mainly been found for the hippocampal formation and the prefrontal and superior temporal lobe [18]. These regions have also been implicated in imaging studies [19]. Ventricular enlargement, reductions in brain volume and changes of cortical thickness, gyrification, hippocampal shape and cerebral asymmetry, which are observed in unmedicated first-episode schizophrenic patients suggest a result of an early neurodevelopmental cascade [19]. Signs for disturbed neuronal connectivity and migration deficits are aberrantly located and neurons cluster in schizophrenic patients in the entorhinal cortex and neocortex [20-22]. A loss of nonneuronal elements, the so-called neuropil, acts as a correlate of brain atrophy. This reduction in neuropil is mainly caused by synaptic elements [21, 22].

Indeed, a mother´s infection during pregnancy -in particular in the second trimenon- or the occurrence of perinatal or postnatal complications has been connected to the development of schizophrenia in the offspring [23]. Also, a fivefold greater risk of developing psychosis has been observed after CNS infection in early childhood, or hypoxic conditions during birth [23]. Interestingly, more than 50% of genes implicated in schizophrenia are also subject to regulation by hypoxia e.g. AKT1, BDNF, CAPON, CCKAR, CHRNA7, CNR1, COMT, DNTBP1, GAD1, GRM3, IL10, MLC1, NOTCH4, NRG1, NR4A2/NURR1, PRODH, RELN, RGS4, RTN4/NOGO and TNF-alpha [24].

The dopamine hypothesis of schizophrenia

The most widely considered neurochemical hypothesis of schizophrenia is the dopamine hypothesis, which postulates that symptoms of schizophrenia may result from excess dopaminergic neurotransmission particularly in mesolimbic and striatal brain regions, leading to positive symptoms and dopaminergic deficits in prefrontal brain regions, which are responsible for the negative symp-

toms. The caudate dopamine D2 receptor up-regulation has been related to the genetic risk for schizophrenia; i.e. higher dopamine D2 receptor density in caudate was associated with poorer performance on cognitive tasks involving corticostriatal pathways [25].

Additionally, all common antipsychotic medications are antagonists or partial agonists of the dopamine D2 receptor, which is the main site of action [26]. Beside a central role of dopamine D2 receptors in effective psychopharmacological treatment, these results provide strong evidence that dopamine D2 receptor influences susceptibility to schizophrenia [27]. Neuroimaging evidence also indicates that schizophrenic patients have increased brain dopamine D2 receptor density [28].

A consistent association exists between the A2 allele of the Taq 1A polymorphism of the dopamine D2 receptor (DRD2) gene and schizophrenia [29, 30], but also the Ser311Cys polymorphism revealed some positive associations although several studies with this polymorphism did not reveal significant results [31-33]. However, from all 24 published case-control studies a meta-analysis was done to examine a possible association of the DRD2 polymorphism with schizophrenia, which showed partly significant results (p=0.007) [27]. Concerning the -141 C Ins/del polymorphism of the DRD2 gene heterogenous data have been found with positive [33-37] and negative findings [32, 38]. The C957T polymorphism affects striatal dopamine D2 binding in healthy subjects [25] and an association between the C957T variant and schizophrenia has been reported that exceeds the magnitude of other findings examining DRD2 polymorphisms [39, 40].

D3 receptors are highly localized in limbic brain areas, which are also related to symptoms of the disease and emotional functions of the brain and the role of D3 receptors in schizophrenia has been implicated in effective treatment [41] but also in the pathophysiology of tardive dyskinesia [42]. The Ser9gly genotype of the D3 receptor has been strongly associated with schizophrenia [43] and was linked to the severity of symptoms on admission [44] and treatment dependent changes [44, 45]. Meta-analyses indicate that the dopamine D3 receptor gene may have a very small influence on risk for the development of schizophrenia [46].

Svenningsson et al. found that a dopamine and adenosine 3',5'-monophosphate (cAMP)-regulated phosphoprotein of 32 kDaltons (DARPP-32) is phosphorylated at three sites in a pattern predicted to cause a synergistic inhibition of protein phosphatase-1 (PP1) and concomitant regulation of its downstream effector proteins glycogen synthase kinase-3 beta (GSK3 beta), cAMP response element-binding protein (CREB) and c-Fos [47]. In mice with a genetic deletion of DARPP-32 or with point mutations in phosphorylation sites of the DARPP-32 gene, the effects of D-amphetamine, LSD, and PCP on sensorimotor gating and repetitive movements were profoundly attenuated [47]. Importantly, there is now a large body of evidence that supports a key role for DARPP-32-dependent signaling in mediating the actions of multiple drugs of abuse including cocaine, amphetamine, nicotine, caffeine, LSD, PCP, ethanol and morphine [47]. A postmortem study reported a significantly reduced DARPP-32 expression in the dorsolateral prefrontal cortex of schizophrenic patients [48]. However, a recent study in 249 schizophrenic patients failed to yield association with five distinct DARPP-32 gene variants [49].

Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin growth factor family, promotes the development, regeneration, and survival of neurons and has therefore been linked to the neuropathology of schizophrenia. BDNF plays a critical role in the development of mesolimbic dopaminergic-related systems and regulates the expression of dopamine D3 receptors [50]. Thus, the hypothesis of a link between BDNF neurotrophic properties and the dopamine neurotransmission pathway in schizophrenia has been postulated [51]. Indeed, in a meta-analysis performed in large samples an association between the C270T polymorphism of the BDNF gene and schizophrenia was observed but no association was found for the G196A polymorphism [52]. However, also the Val66Met polymorphism of BDNF does not seem to be associated with schizophrenia in a recent meta-analysis [53].

The glutamatergic hypothesis of schizophrenia

Several lines of evidence point to the hypothesis that dopaminergic dysfunction in schizophrenia is secondary to an underlying glutamatergic dysfunction. In this concept a hypofunction of glutamate in cortico-striatal projections leads to an opening effect in the thalamo-cortical loop resulting in an exaggerated sensory flooding and thereby psychotic symptoms and the well-known dopamine concentration changes. The glutamate receptors consist of two groups: ionotropic ligand-gated ion-channels and metabotropic G protein-coupled receptors. The ionotropic receptors can be subdivided into the alpha-amino-3-hydroxy-5-methyl-4-isoxazole-

propionic acid (AMPA) Kainate and N-methyl d-aspartate (NMDA)-receptors [54]. These ionotropic glutamate receptors work as ion-channels by opening in response to glutamate binding and creating a depolarising excitatory post-synaptic current. NMDA receptors are tetrameric allosteric and ligand-gated calcium channels, which are modulated by a variety of endogenous ligands and ions that play a pivotal role in memory-related signal transduction due to a voltage-dependent block by magnesium. NMDA receptors are thought to be responsible for excitotoxicity and subsequent downstream events such as neuroinflammation and apoptosis. The NMDA receptor is composed of three different subunits, NR1 (GRIN1), NR2 (GRIN2A and GRIN2B) and NR3 (GRIN3). NR1 is the binding site for the co-agonists glycine and D-serine, NR 2 is the agonist binding site for glutamate [55]. NR3A subunits are known to act as dominant negative regulators of the NMDA receptor current and they have been shown to alter the two most prominent properties of the NMDA receptor: calcium permeability and magnesium sensitivity. A study in humans indicates that genetic variation of this subunit determines prefrontal cortex activity during an attention task [56].

In line with the glutamate hypothesis, NMDA-receptor antagonists like phencyclidine, ketamine and MK-801 are potent activators of dopamine release and thereby can cause marked psychotic symptoms in healthy human volunteers and exacerbation of symptoms in schizophrenic patients [57, 58]. A loss of glutamatergic function in schizophrenia is also supported by decreases in markers for the neuronal glutamate transporter in striatal structures that receive cortical glutamate projections. Deficits in the vesicular glutamate transporter-1 in both striatal and hippocampal regions support this observation, and the association of the transporters´ density with the risk to develop schizophrenia [59].

Beside glycine, D-serine is a potent activator of the NMDA receptors, which has properties of a neurotransmitter [60]. D-serine is synthesized from L-serine depending on several co-factors such as pyridoxal 5-phosphate (vitamin B6), magnesium and adenosine 5'-triphosphate (ATP) [61-63]. Therefore, increased availability of glycine or serine may facilitate glutamatergic neurotransmission [54]. In support of this inference, agents that directly or indirectly activate the glycine or serine modulatory site on the NMDA receptor, i.e. D-serine, glycine, D-cycloserine and N-methylglycine reduce symptoms in chronic schizophrenia, especially negative symptoms and cognitive impairments [64-66]. A reduction of D-serine serum levels of schizophrenic patients was also shown [67].

Most recently the first highly interesting selective agonist for metabotropic glutamate 2/3 (mGlu2/3) receptors (LY2140023) has been developed, which is the first drug not acting as dopamine antagonist [68]. This drug shows improvement of positive and negative symptoms that are comparable with olanzapine but fails to produce prolactin elevation, extrapyramidal symptoms or weight gain [68].

Former data suggested that a genetic variant of the serine racemase gene might be associated with the disease [69]. However, in two consecutive genetic studies it was concluded that serine racemase is not a major contributing gene to the pathophysiology of schizophrenia [67, 70].

Regarding glutamate transporter genes SLC1A1, SLC1A3, and SLC1A6 encoding the glutamate transporters EAAT3, EAAT1, and EAAT4, in a Japanese sample a positive connection with schizophrenia has been found nearby SLC1A6, whereas SLC1A1 and SLC1A3 were unlikely to be major susceptibility genes for schizophrenia [71]. Furthermore, an association study of the glutamate transporter 2 gene, SLC1A2 with schizophrenia was reported [72].

In 2455 Han Chinese subjects 2 NMDA receptor subunit genes, GRIN1 and GRIN2A have been studied. As a result a highly significant association with schizophrenia was found for polymorphisms of the 5' end of GRIN1, but not for GRIN2A polymorphisms [73]. In a current meta-analysis GRIN2B resulted in a statistically significant association with schizophrenia, which supports the involvement of the glutamate system in the pathogenesis of schizophrenia [74]. The GRIA1 gene encodes for one (GluR1) of the four ionotropic AMPA receptor subunits and has been found to be decreased in the brain of some schizophrenic patients. It has also been connected with genetic susceptibility for schizophrenia [75].

Several lines of evidence implicate neuregulin 1 (NRG1) and its receptor ErbB4 (V-erb-B2 avian erythroblastic leukaemia viral oncogene homolog 4 receptor) to be involved in schizophrenia [76, 77]. In line with the glutamate hypothesis of schizophrenia, activation of NRG1 promotes rapid internalization of NMDA receptors from the cell surface by a clathrin-dependent mechanism in prefrontal pyramidal neurons [78]. Also, overactivation of the V-erb-B2 avian erythroblastic leukaemia viral oncogene homologe 4 receptor (ErbB4) by NRG1 leads to reduced tyrosine phosphorylation of NR2A in the prefrontal cortex of patients with schizophrenia [79],

which could suppress NMDA receptor activity. Recently, a genetic variant in the human NRG1 promoter region in subjects at high risk of schizophrenia has been shown to be associated with decreased activation of frontal and temporal lobe regions, increased development of psychotic symptoms and decreased premorbid IQ [80]. A novel missense mutation of NRG1 in the transmembrane domain (Val to Leu in exon 11) has been associated with schizophrenia [81], whereas two SNPs in the 3' region of the NRG1 gene yielded suggestive evidence for association in a family-based association analysis [82]. In a meta-analysis of 13 published population-based and family-based association studies, the involvement of NRG1 in the pathogenesis of schizophrenia has been corroborated [77]. Interestingly, the behavioural effects of tetrahydrocannabinol (THC) are modified in heterozygous NRG1 transmembrane-domain knockout mice [83].

Dysbindin (DTNBP1, Dystrobrevin Binding Protein 1) is widely expressed in the human brain and appears to play an important role in cognitive functioning and memory [84]. It has been speculated that dysbindin-1 among others maintains glutamatergic neurotransmission [85]. Its function in presynaptic, postsynaptic and microtubule locations has been related to snare-associated protein snapin, its binding partner in the brain [86]. Postmortem studies suggest that dysbindin concentrations in the brain are reduced in individuals with schizophrenia [87], and carriers of a genetic variation in the dysbindin-1 gene have demonstrated a functional decline in IQ compared with non-carriers [88].

Several genetic studies involving different populations have found positive associations of dysbindin with schizophrenia [89-93]. However, no variant of dysbindin has been constantly linked to schizophrenia, i.e. allelic heterogeneity is demonstrated which refers to different disease causing mutations in the same gene. Across different studies, the risk conferred by any dysbindin variant is small [94]. Moreover, an allele might be associated with increased disease risk in some studies and decreased risk in others [84]. Nevertheless, an exception is given by SNP rs1047631, which has been associated with differences in the expression of dysbindin in the brain [90]. The most favoured interpretation of these data is currently, that dysbindin variants mediate the course of the disease [94].

Chumakov, who firstly discovered D-amino acid oxidase (DAAO or DAAOX) and G72, demonstrated that the G72 protein activates DAAO protein [95]. DAAO oxidizes D-amino acids, especially proline, methionine and alanine but also D-amino acids like D-glutamate and D-aspartate, which are poorer substrates for DAAO [96]. DAAO is relevant in NMDA receptor signaling [96]. DAAO knockout mice have increased D-serine levels in the cerebellum and the medulla but no change in D-serine levels in the forebrain [96]. Morphine administration produced a dose-dependent and transient elevation of mRNA expression of DAAO in all the brain areas which suggested an interaction between the mRNA expression of D-serine-related enzymes and opioid receptor activation [97]. Consistent with this, exaggerated pain behaviour has been observed in DAAO knockout mice [98].

In contrast to DAAO, which in rodents shows scarce activity in the forebrain but strong activity in the astrocytes of the brainstem and the cerebellum, G72 is preferentially expressed in brain regions associated with schizophrenia. In this context, Korostishevsky et al. showed increased G72 expression in the dorsolateral prefrontal cortex of schizophrenia patients as compared to healthy controls [99, 96].

The DAAO gene is furthermore of higher interest as susceptibility gene for schizophrenia due to its location on chromosome 13q22-34, a region that was implicated in schizophrenia through linkage analyses [95].

A potential role in glutamatergic neurotransmission and schizophrenia was postulated for both, G72 and DAAO genes [84, 96, 100, 101], but it has also been suggested that DAAO and G72 genes are not susceptibility genes for schizophrenia [102, 103]. Perhaps a subgroup of schizophrenic patients, namely patients experiencing "persecutory delusions" [104] or patients with episodic memory deficits [101] might have affections due to DAAO and/or G72 genotype.

Also, for genetic variation of glutamate receptor type 3 gene (GRM3) an influence on cognition, prefrontal glutamate, and risk for schizophrenia has been shown [(rs187993) 105, 106], although for other SNPs negative results have been obtained, i.e. rs917071, rs6465084, rs2228595, rs1468412 [105] and rs187993 [107]. Several other studies on different polymorphisms on GRM3 displayed partly positive [106, 108-112] and partly negative findings [76, 107].

The GABAergic hypothesis of schizophrenia

There is an accumulation of evidence for abnormalities in schizophrenia of both glutamate and gamma-aminobutyric acid (GABA) [59]. The 67 and 65 kDa isoforms of glutamic acid decarboxylase (GAD), the key

enzymes for GABA biosynthesis, are expressed at altered levels in postmortem brain of subjects diagnosed with schizophrenia. A decrease in GAD67 transcript levels has presumably been found in prefrontal and temporal cortex [113]. The promoter of GAD1 (2q31), the gene encoding GAD67, has been linked to schizophrenia [115, 114], leading to disordered connectivity in concert with abnormal expression of Reelin and neural adhesion molecule glykoproteins [114]. Accordingly, Reelin has been stated as one of the genetic variants contributing to the risk of the disease [116]. In a recent study by Benes et al. a unique network consisting of 12 different genes that may be involved in the regulation of GAD67 expression in human hippocampus has been evolved in schizophrenia [117]. An investigation on a group of GABAA receptor subunit genes (GABRA1, GABRA6, GABRB2, GABRG2, and GABRP) revealed associations in a Portuguese patient sample of SNPs in GABRA1, GABRP and GABRA6 [118] with schizophrenia. The GABRA1 and GABRP findings were replicated in an independent German family-based sample [118].

As one of the key susceptibility factors, Disrupted-in-schizophrenia (DISC1), has been established as a promising lead in the understanding of the disease [119,21]. DISC1 is involved in neurite outgrowth and neuronal migration [120-122,] and is expressed in brain regions, which are known to be involved in schizophrenia, including human cerebral cortex and hippocampus [21, 123, 124]. Also, DISC1 plays a role in cell signaling and interacts with phosphodiesterase 4B, which degrades cAMP, which may be a regulatory molecule for working memory in the prefrontal cortex [125]. DISC1 interacts with a number of proteins, including centrosome and cytoskeletal proteins, proteins that localize receptors to membranes, and signal transduction proteins [121, 126]. The location of DISC1 at many synapses suggests that it may play a role in synaptic function in the adult brain [21, 124]. The amount of DISC1 peaks in the mouse brain during the time of embryonic neurogenesis and again during puberty [127, 128,], two critical time points also implicated in vulnerability to and manifestation of schizophrenic symptoms. Usually Nude-like protein (NUDEL), which is a protein essential for cortical development, neuronal migration, and axonal growth binds to DISC1. NUDEL is reduced in hippocampus and prefrontal cortex of subjects with schizophrenia [129]. If the interaction of NUDEL and DISC1 is disturbed, neurite outgrowth is inhibited and results in abnormal cortical development in vivo [130, 131].

DISC1 was originally found through breakpoint mapping in an extended family in which a balanced chromosomal translocation on chromosome 1q42 co-segregated with psychiatric disorders including schizophrenia, bipolar disorder and recurrent major depression [132]. A number of confirmatory linkage and association studies has been performed since then [133]. The studies indicate that DISC1 is a general genetic risk factor for psychiatric illness that also influences cognition in healthy subjects [133]. It has been shown that psychiatric diagnosis of schizophrenia, reduced frontal cortical gray matter and performance on neurocognitive tests of short and long-term memory are associated with aberrant expression of the DISC1 gene [134]. Further, it has been suggested that the effect of DISC1 genetic variation might be associated with positive symptoms and hippocampal volume in patients with schizophrenia [135, 136]. Also, sustained attention deficits in a Taiwanese schizophrenic sample have been associated with the DISC1 gene [103].

Chowdari et al. have catalogued common regulators of G-protein signaling (RGS4) polymorphisms and observed extensive linkage disequilibrium in this region [137]. Twenty-eight RGS proteins have been identified today [138, 139], which function as GTPase-activator proteins for heterotrimeric G-protein alpha (Gα) subunits and accelerate the hydrolysis of Gα-bound GTP [139]. Thus, they shorten the duration of intracellular G-protein–coupled receptor signaling and thereby modulate intracellular effects of G-protein-coupled neurotransmitters [137-139]. RGS4 has been shown to be regulated by stress and glucocorticoids and RGS4 mRNA levels were significantly lower in postmortem samples of the dorsolateral prefrontal cortex of subjects with schizophrenia compared with matched controls [140].

Consecutively, several genetic association studies on a role of RGS4 in schizophrenia have been performed in the past years [137, 140-146]. In a meta-analysis of Talkowski et al. [145] a positive result due to at least two common haplotypes have been reported although a smaller meta-analysis failed to detect an association between this glutamate-related gene and schizophrenia could be shown [77].

22q11.2 deletion syndrome

A deletion of 22q11.2 causing the most common microdeletion syndrome with an estimated prevalence of 1:2500-1:4000 live births, increases the risk of schizophrenia up to 30 percent of affected individuals [12, 147]. Linkage disequilibrium mapping at chromosome 22q11 in

patients identified a segment containing two genes, proline dehydrogenase (PRODH) and DiGeorge syndrome critical region gene 6 (DGCR6) as candidates [103], and by analysis of additional polymorphisms the PRODH gene was found to be associated with schizophrenia in adult and early onset patients. An implication of PRODH was also replicated by Li et al. in a Chinese population [74]. Systematic examination of individual genes from the 1.5 Mb critical region have also identified the genes for PRODH and zink finger DHHC domain-containing protein 8 (ZDHHC8) as strong candidate for schizophrenia [148]. Polymorphisms of the DGCR2 gene, which encodes a putative adhesion receptor protein was also found to be associated with schizophrenia in an independent sample [149]. This association was confirmed between DGCR2 and schizophrenia through individual genotyping of 1,400 subjects. Interestingly, the expression of DGCR2 in the dorsolateral prefrontal cortex was found to be elevated in schizophrenic patients relative to matched controls [149], which was also shown in rats exposed to antipsychotic medication [149]. The discovery of these genes implicates neuromodulatory aminoacids and protein palmitoylation as important for disease development.

Along with 47 other genes, catechol-O-methyl transferase (COMT) is located in this region, which is a catabolic enzyme involved in the degradation of a number of bioactive molecules, particularly dopamine [150]. COMT has been shown to be critical for prefrontal dopamine flux as well as prefrontal cortex-dependent cognition and activation [3, 106]. Several COMT polymorphisms substantially influence the activity of the enzyme [150]. However, the relationship between COMT polymorphisms and schizophrenia is complex and makes it impossible to draw strong, direct conclusions as dopamine availability and brain functioning is not a linear function [150].

In a longitudinal study of adolescents with 22q11.2 deletion syndrome, COMT Met allele was identified as a risk factor for decline in prefrontal cortical volume and cognition, as well as for the consequent development of psychotic symptoms during adolescence [151]. In contrast, the Val allele has been connected especially with high scores of positive dimensions measured by the Schizotypal Personality Questionnaire in a sample of 106 unaffected subjects [152].

However, there exists controversy regarding the contribution of individual alleles and haplotypes to risk for schizophrenia [153, 154], as also negative findings regarding the role of COMT in schizophrenia have been published [46, 155]. Interestingly, in a statistical meta-analysis an interaction between COMT and polymorphisms in several candidate genes for schizophrenia (i.e. RGS4, G72, GRM3, DISC1, many of which had no significant main effect itself) has been reported [156].

Linking Phosphatidylinositide 3-kinase (PI3K) pathway to schizophrenia

PI3K is involved in cellular processes that are central to the development of schizophrenia such as cell growth, cell differentiation, cell migration, axonal sprouting and cell survival [157, 158]. Erythropoietin [159], BDNF [160], NRG1 [161], Reelin [162], NGF [163] and dysbindin [164] have been discussed to protect schizophrenic patients from cognitive decline and deterioration of the disease. All of these proteins together with substances, which have been implicated in the treatment of the disease, i.e. estrogen [165, 166], insulin [167], haloperidol [168,], risperidone [169] and clozapine [169] have been shown to act via PI3K signaling. Downstream targets of PI3K are V-akt murine thymoma viral oncogene homologue (Akt), glycogen synthase kinase (GSK3Beta), Beta Catenin and CREB, which had all been involved in the pathophysiology of the disease based on protein, mRNA and enzyme activity changes [168, 170-172]. Increased apoptosis due to abnormalities in Akt signaling could contribute to the pathophysiology of schizophrenia [173-175]. The examination of different haplotypes of Akt, the most important downstream target of PI3K revealed mostly positive results [168, 176-178], however, also weak positive [175] and negative data exist [82, 179]. In the light of the recent replications, the evidence for Akt as a susceptibility gene for schizophrenia is encouraging and warrants further investigation [173, 175].

However, in contrast to convincing data on the protein level, the examination of polymorphisms of GSK-3Beta revealed no significant association between this polymorphism and schizophrenia in chinese patients [180] and in a small European sample GSK-3Beta appears to be involved in the paranoid subtype of schizophrenic patients, but not in schizophrenia in general [181]. Concerning CREB novel variants of the gene have been found only in schizophrenic patients [182], but replication studies are pending.

The immune hypothesis of schizophrenia

Epidemiological data point to an association between schizophrenia and influenza, and additionally signs of in-

flammation in schizophrenic brains have been found bridging the disease to a "mild localized chronic enzephalitis" [183, 184]. Infection of mothers during pregnancy is associated with the development of schizophrenia in the offspring [185, 186], and a recent meta-analysis, that summarized seven studies including only patients with first-episode schizophrenia and 16 studies including patients in all clinical phases, resulted in an increased prevalence of antibodies to Toxoplasma gondii in individuals with schizophrenia [187].

In preliminary studies, in patients with schizophrenia production of interleukin 2 (IL-2) and interferon gamma (IFNG) was shown to be reduced, resulting from a blunted type 1 immune response [184]. This hypothesis might be underpinned by the finding of decreased soluble intracellular adhesion molecules (ICAM) [188] and decreased response of lymphocytes after stimulation [184].

On the contrary, type 2 immune response in schizophrenic patients has been hypothesized to be increased [189]. Signs, which point to this activation are increased levels of IL-6 [190], increased production of immunoglobulin and an increase in levels of IL-10 and IL-4, which are possibly elevated in CSF of schizophrenic patients [184]. Functional consequences of a type 2 activation in schizophrenia are an imbalance between indoleamine 2,3 dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) [184] and a concomitant upregulation of astrocytes. Both mechanisms modulate kynurenic acid (KYNA), the only naturally occurring NMDA receptor antagonist. Parameters of an imbalance between type 1 and type 2 immune responses in schizophrenia seem to normalize partly after antipsychotic therapy [191]. In a clinical study, utilizing COX-2-inhibitors, which seem to rebalance the type1/type2 shift by inhibition of IL-6 and prostaglandin E2 and stimulation of type 1 immune response, celecoxib was successful as add-on therapy especially regarding cognitive functioning in schizophrenic patients [192].

In a genetic association study of several candidate cytokine genes, namely IL-1B, IL-1 receptor antagonist (IL-1RN), and IL-10 and an additionally performed meta-analysis combined with previously published association studies, IL-1B was suggested to play a role in predisposition to schizophrenia in 819 Caucasians but not in the Asian population [193]. The IL-1RN polymorphism has been connected to improvement of negative symptoms and clinical improvement during antipsychotic treatment in patients with a first non-affective psychotic episode [194]. Polymorphisms of IL-1B and IL-1RN showed an association with a significant enlargement of both ventricles in schizophrenic patients [195]. Moreover, IL-2 and IL-4 polymorphisms could be identified to be significantly associated with schizophrenia [196].

Conclusions

Schizophrenia is a complex disorder, which is not simply defined by several major genes but rather evolves from addition or potentiation of a specific cluster of genes, which subsequently determines the genetic vulnerability of an individual. Being genetically vulnerable however, is not forcefully leading to the disease, triggering factors and environmental influence lead to the assumption, that schizophrenia is not only a genetically defined static disorder but a dynamic process leading to dysregulation of multiple pathways. The pathobiological cascade of schizophrenia is far from understood. There are several different hypothesis based on several facets of the disease, some of them due to well-known mechanisms of therapeutic agents (e.g. dopamine hypothesis). Increasing clinical and basic knowledge is even linking schizophrenia to bipolar disorder, suggesting that our classification system is not highly selective concerning different clinical and biological distinct subgroups of both diseases. Moreover, examined samples of schizophrenic patients might actually include several different biological subtypes, as symptoms and course of the disease are highly variable in different patients.

Often different workgroups specialize on one area of interest and prefer a specific point of view, or even a single gene or receptor. However, molecular findings suggest that a complex interplay between receptors, kinases, proteins and hormones is involved in schizophrenia, so in a unifying hypothesis different cascades might merge into another. However, the pathways discussed above will be involved to a more or lesser extent in disease onset, symptom development, and therapeutic control. Further research is needed to elucidate interfering factors and interconnectivity of the involved systems. The final goal is to unravel the mystery of schizophrenia, to detect patients in early stages of the diseases and to implement therapeutic strategies that lead to full recovery of symptoms.

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