NRG1 Gene Mutation and Treatments Related to Schizophrenia

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Abstract: Schizophrenia is a serious mental disease that accounts for 0.5-1% of the world's population. Patients with this disease show positive symptoms (hallucination and delusion) and negative symptoms (lack of emotion, behavior, and language deficits). Both physical and genetic factors can cause schizophrenia, with the latter confirmed in multiple studies. Several candidate genes that play roles in regulating brain activities were indicated to contribute to the disease. Patients with mutations on these schizophrenia-related genes were observed to have developmental and anatomical abnormalities in their brains. The gene of NRG1 is the only one to be identified in both meta-analyses and genome-wide linkage scans. Therefore, in-depth studies on the relationship between NRG1 and schizophrenia are suggested to be conveyed. NRG1 is a trophic factor that activates ErbB receptor tyrosine kinases. NRG1-ErbB signaling functions in both brain development and adult brain, whose perturbation may lead to cognitive impairments and other symptoms observed in patients with schizophrenia. In this article, the disease of schizophrenia will be introduced from different aspects, including its clinical manifestations, its harm, and causes. NRG1 and NRG1-ErbB signaling functions in the brain and how mutations in the coding region of NRG1, generated by single nucleotide polymorphisms (SNPs), are related to schizophrenia analyzed. The treatments of schizophrenia are classified as pharmacological therapies and nonpharmacological therapies. Studied on the novel genetic therapy of CRISPR will also be mentioned.

1. Introduction

Schizophrenia is a very serious mental disease, which will greatly impact patients' lives and may lead to death. So far, there are still many unknowns in causes and effective treatments for schizophrenia. Current research shows that schizophrenia is closely related to genetic abnormalities. At present, we have a clear understanding of the relationship between the NRG1 gene and disease. The normal NRG1 gene is a necessary condition for the normal function of the nervous system. The abnormality of the NRG1 gene will lead to many mental diseases. Schizophrenia is also closely related to the abnormality of the NRG1 gene, so we think through the study of NRG1 gene mutation, we can get the cause of schizophrenia.

At present, scientists are looking for a treatment for schizophrenia. However, many treatments cannot fundamentally solve the problem, so we hope to treat it genetically. We want to use CRISPR technology for treatment. CRISPR is a repetitive sequence in prokaryotic organisms. CRISPR technology can delete and correct wrong genes, so we try to build a guide RNA and use CRISPR technology to treat schizophrenia.

2. Profile Of Schizophrenia

2.1 The concept of schizophrenia

Schizophrenia has individual personality change, thinking mode change, behavior, and emotional split as the main characteristics, and accounts for about 0.5% - 1% of the total population in the world [1]. Most people with schizophrenia are between eighteen and thirty years old, and more male patients than female patients.

Although the incidence of schizophrenia is not high, the harm of schizophrenia should not be ignored, so we should make an in-depth study of the causes and the symptoms of the disease.

2.2 Main clinical manifestations of schizophrenia

The main symptoms of schizophrenia can be divided into two main categories, including positive symptoms and negative symptoms.

The positive symptoms, also the most common clinical manifestation of schizophrenia, includes hallucination and delusion, which means they may feel nonexistent things and imagine something that won't happen. Patients with schizophrenia often have auditory hallucinations, phantasmagoric smell, phantasmagoric, and other sensory disorders. While many mental illnesses cause hallucinations, the ones that people with schizophrenia have tended to be unique in that they may hear people scolding them and giving them orders. They may also have delusions, including persecutory, referential, somatic, erotomaniac, religious, and grandiose delusion. For example, they may think that other people are talking about him or her, and they may often feel guilty. Sometimes the patients may think they are being watched, and they may be murdered.

The representative of negative symptoms is lack of emotion. According to the survey, schizophrenia patients with prominent negative symptoms showed more deficits in anticipatory pleasure, especially in abstract anticipation [2], than normal people. Behavioural and language disorders are also common clinical manifestations. Patients with schizophrenia often have logical jumps that ordinary people cannot understand, so their behaviour and language are always confused.

Besides, the patient may also have high mental stress and may experience manic and depressive symptoms, making sufferers lose the ability to live and seriously affect their health.

2.3 The harm of schizophrenia

Schizophrenia has very serious harm. We found that self-suicide is the main character of the patient. According to the survey, hallucinations are significantly associated with suicidal ideation, especially the content or voice that belittles and injures the self. Depression increased the sense of hopelessness and was associated with suicide [3]. A meta-analysis [4] showed that the prevalence of suicidal thoughts in Chinese patients with schizophrenia was 25.8%. In comparison, the number of patients who died by suicide was 5%, and 25% ~ 50% of patients had attempted suicide in their lifetime [3]. Suicide rates are 50 to 100 times higher in people with schizophrenia than in general people. Therefore, it is very necessary to study the etiology of schizophrenia and seek treatment.

2.4 Causes of schizophrenia

Many factors are leading to schizophrenia, such as physical factors. One study concluded that 21–65% of individuals with schizophrenia [5] had experienced childhood sexual or physical abuse. Studies show that delay and persist for a long time due to sudden, threatening, or catastrophic life events [6] may cause post-traumatic stress disorder (PTSD). PTSD worsens the clinical outcome of severe mental disorders by enhancing hyper-arousal, 65 dissociation, and reexperiencing symptoms. These latter expressed as trauma-based hallucinations [7].

Genetic factors are also important causes. Epidemiological studies from the beginning of the 20th century and the emergence of new research results and evaluation criteria have shown the importance of genetic factors in schizophrenia [8]. According to the survey, the prevalence of schizophrenia in offspring was 12% when one parent had schizophrenia and 39% when both parents had schizophrenia. It indicates that genetic factors or genetic background play an important role in

developing schizophrenia [9]. Lipska and Weinberger were the first to evaluate how the genetic background moderates the effects of early brain injury that leads to behavioral schizophrenia-like abnormalities in rats [10]. According to their survey, Lewis rats having lower HPA axis and mesolimbic DA functions with lower emotional reactivity and higher sensitivity to the reinforcing effects of drugs compared to F344 rats [11]. That indicated the gene factor (different rat strains) would lead to schizophrenia.

Gene can affect the development of schizophrenia in many ways. For example, it has been proved that the COMT genetic variation may affect the abnormal secretion of dopamine and have downstream implications for the regulation of brainstem DA activity [12], which are important for maintaining normal brain activity.

Besides gene mutation associated with the abnormal development of the brain, neuropathological studies show that patients with schizophrenia usually have the shrinkage of the limbic system and temporal lobe, cell structure disorder of hippocampus and frontal cortex, which may be related to a cognitive impairment such as executive function, which may be related to a cognitive impairment such as executive function [13]. So, it is important to research genetic factors leading to schizophrenia.

3. NRG1 And Schizophrenia

3.1 Background of gene and disease

The susceptibility to schizophrenia that was influenced by genetic factors has been well established [14]. Candidate genes that contribute to the disease had been revealed as dysbindin (DTNBP1), neuregulin 1 (NRG1), G72, a regulator of G-protein signaling 4 (RGS4), catechol-O-methyl transferase (COMT), proline dehydrogenase (PRODH), metabotropic glutamate receptor 3 (GRM3), protein kinase AKT1 (AKT1) and disrupted-in-schizophrenia 1 (DISC1) [14]. However, many studies failed to replicate the positive findings with respect to most of the listed genes due to various reasons, such as the lack of linkage disequilibrium (LD) between the susceptibility allele and SNPs used in the study, genetic heterogeneity, and true lack of association [15]. Of those candidate schizophrenia susceptibility genes, only NRG1 was identified in both meta-analyses and genome-wide linkage scans [14].

3.2 Introduction of NRG1 and the function of the protein

In the year 2002, Stefansson and colleagues presented the results, carried out in Iceland, of a genome-wide scan for linkage to schizophrenia, followed by mapping at a locus on chromosome 8p. Haplotype analysis suggested NRG1 as a candidate gene for schizophrenia, which played a role in the pathogenesis of the disease. In this original association study, five single nucleotide polymorphisms (SNPs) and two microsatellites were over-represented in patients with schizophrenia than controls, collectively named 7-marker NRG1 ‘high-risk’ haplotype (HAPICE). SNP8NRG221533 (T to C SNP) was considered the most significant SNP [16]. Follow-up studies in multiple ethnic populations and a meta-analysis have confirmed the genetic association between schizophrenia and NRG1 using markers within the same core haplotype or with overlapping markers in the 5′ region [17].

For the original HAPICE (now referred to as ‘deCODE’ haplotype), SNP8NRG221533 and two other SNPs in NRG1 were then, soon after, reported in another study of Chinese Han schizophrenia family trios. The claim of NRG1 as a schizophrenia-susceptibility gene was confirmed in studies done with multiple populations in Scotland, Ireland, the United Kingdom, the Netherlands, and Korea, even though studies of Japanese, Irish, Spanish populations showed a poor genetic association between NRG1 and schizophrenia [18].

NRG1 is a trophic factor that contains an epidermal growth factor (EGF)-like domain, locating in the membrane-proximal region of the extracellular domain, which is essential for activating the ErbB receptor tyrosine kinases. Due to the usage of distinct 5' flanking regulatory elements and alternative splicing, six types of protein (I-VI) and at least 31 isoforms (Neu differentiation factor (NDF),

heregulin, glial growth factor (GGF), acetylcholine-receptor-inducing activity (ARIA)) can be generated by NRG1 [18]. These isoforms differ in their tissue-specific expression patterns, biological activities, and thus, in vivo functions [19]. Some NRG1 isoforms are evidenced to be abnormally expressed in patients with schizophrenia.

NRG1-ErbB signaling is found to be importantly involved in brain development [18, 20]. Loss-of-function mutation at the level of NRG1 or dysfunction of NRG1 signaling can cause deficits in pyramidal and GABAergic neurons migration, neurite outgrowth in primary neurons of different kinds (hippocampal neurons, retinal neurons, cerebellar granule cells, and thalamic neurons), axon projection, as well as myelination of axons and synapse formation [18]. To be more detailed, NRG1 serves as an axon-derived signal for oligodendrocyte development, promoting the proliferation and survival of those cells [21]. NRG1, in the first place, enhances the differentiation of oligodendrocyte from bipotential glial progenitor cells, evidenced by its expression in the subventricular zone of rats' brains at the critical time of this differentiation [21]. NRG1, specifically NRG1 Type III isoform, also promotes Schwann cell proliferation and differentiation [22]. In 2006, Nave and colleagues suggested the level of Type III NRG1 in the axon as a key instructive signal for myelination [23]. In the CNS, Type III NRG1 influences the expression level of acetylcholine receptors (AChRs), whereas Type I and Type II isoforms alter the expression of GABA receptors [24]. The signaling stimulated by all three types of isoforms alters the profiles of various glutamate receptors (NMDA and AMPA receptors). The differential regulation of glutamate receptors depends on the NRG1 isoforms expressed [25].

The functions of NRG1-ErbB signaling in brain development are consistent with the 'abnormal neural development' model of schizophrenia which is mostly viewed as a disorder of development [20]. The resulting anatomical abnormalities would potentially cause changes in neurotransmission in the brain and cortical function, leading to cognitive impairments and other psychotic symptoms observed in patients with schizophrenia [20].

NRG1-ErbB4 signaling also functions in the mature nervous system. By analyzing the expression patterns of different isoforms of NRG1 and ErbB4, NRG1 has been found to regulate both excitatory and inhibitory synaptic transmission in the adult brain [26, 27]. Specifically, in the cortex, NRG1 Type I and Type II isoforms are expressed in layers 2, 3, 6b; NRG1 Type III isoform is expressed in layer 5. All those three NRG1 isoforms are expressed in the reticular nucleus of the thalamus, the piriform cortex, the hippocampus. ErbB4 is also expressed in cortical layers 2−6b. It is present at high in the medial habenula, the reticular nucleus of the thalamus, and the intercalated masses of the amygdala, at which interneurons are enriched [26].

In terms of short-term plasticity, the interaction of ErbB4 and co-localized PSD95 (a postsynaptic scaffold protein that is essential for the assembly and function of glutamatergic synapses) enhances NRG-dependent intracellular signaling, which affects both the induction and the expression of long-term potentiation (LTP) in an endogenous-NRG1-level-dependent manner [25, 28]. NRG1 also directly activating ErbB4 receptors on presynaptic terminals, regulates GABA release, and, thus, the signal integration by pyramidal neurons [29]. The functions of NRG1 imply the working-memory deficits in patients with schizophrenia because the final output of pyramidal neurons is dependent on glutamatergic and GABAergic inputs that are both regulated by NRG1 [18]. NRG1 also plays a role in long-term plasticity and in neuronal survival [18].

3.3 Mutation of NRG1

Meta-analyses of whole-genome linkage scans identified 8p as a susceptibility locus for schizophrenia. Analysis of Iceland families narrowed the region from 8p12 to 8p21, within which NRG1, the candidate gene for the disorder, lies in [16]. SNPs generate changes in the coding region of NRG1. A valine to leucine conservative substitution, identified in the transmembrane region of the NRG1 protein, has unclear functional implications [30].

In 2013, Elliot Hong and colleagues pointed out that the SNP of rs3924999 mutation in the Type-II-NRG1-specific region had a role in causing the prepulse inhibition (PPI) deficits and schizotypal personality in patients with schizophrenia [31]. Rs3924999 is in the 2nd exon of the

NRG1 gene. It is a G to A transition at the 2ndcodon, exchanging arginine (R) to glutamine (Q) in the polypeptide chain. PPI is a widely used surrogate measure of psychosis in animal models like rodents, and it is a neurophysiological endophenotype in schizophrenia. The effects of NRG1 on PPI in rodents are hypothesized to be similar to that in humans. The experiment showed that the percentage of PPI was the lowest in homozygous A/A (or Q/Q) carriers, intermediate in heterozygous A/G (or Q/R) carriers, and the highest in homozygous G/G (or R/R) carriers [31]. A follow-up regression analysis suggested that rs3924999 alone contributed to 7.9% of the PPI variance. The results illustrated the association between reduced PPI in the carriers of rs3924999 mismatch mutation, reflecting the association between a potentially functional variant in the NRG1 gene and the schizophrenia-related endophenotype in humans [31]. This study also showed limited to no association between the rs10503929 mutation (methionine to threonine) and changes in PPI [31].

4. Treatment of schizophrenia

4.1 Pharmacological therapy of schizophrenia

In most cases of schizophrenia treatment, the effect of antipsychotic medication is significant and irreplaceable. This section will look at how antipsychotics take effect and the mechanism that pushes forward the development of pharmacological therapy. Also, we are going to briefly introduce several categories of antipsychotics that are currently used.

1) Mechanism of pharmacological treatment of schizophrenia

The pathway that how antipsychotic drugs (APDS) take effect on schizophrenia symptoms has multiple hypotheses. They mainly include dopamine receptor modulation, serotonin receptor modulation, and NMDA receptor modulation [32].

The most widely accepted model of DA receptor modulation is advanced by Albin et al. Based on the hypothesis that schizophrenia is involved with dysregulation of neurotransmission and excessed dopaminergic activity in the mesolimbic pathway [33]. Based on this hypothesis, all currently used APDs has nanomolar affinity on D2 receptor and can in some degree inhibit the effect of DA.

Serotonin receptor modulation is popularized by Meltzer et al. [34]. It says that the antagonism of 5HT2A can increase dopaminergic transmission in the nigrostriatal pathway. Thus reduce the risk of EPS and increase the release of DA and acetylcholine in the prefrontal cortex. Theoretically, this process can reduce the negative symptom of schizophrenia [32]. This hypothesis explains the treating mechanism of the most second-generation antipsychotics (SGA) medicine (includes asenapine, clozapine, iloperidone, olanzapine, paliperidone, perospirone, quetiapine, risperidone, sertindole, ziprasidone, and zotepine). However, several medicines cannot be fitted in this model. For example, amisulpride has no meaningful affinity for the 5-HT2A receptor, and aripiprazole and blonanserin have higher D2 than 5-HT2A affinity, yet clinically, they are not having atypical profiles [35, 36].

The NMDA receptor modulation model hypothesizes that N-methyl-D-aspartate (NMDA) antagonists can reduce the negative, positive, and other schizophrenia-related symptoms [37-39]. It indicates that NMDA-R can contribute to the pathophysiology of schizophrenia. A wide range of preclinical studies has demonstrated some SGAs' selectively antagonism effect toward experimentally induced NMDA-R hypofunction [40, 41].

2) Currently used medicines

The main medicine categories currently used for schizophrenia therapy treatment are Phenothiazines, Butyrophenones, Thioxanthones, and Dihydroindolone. Overall, those 4 types of neuroleptic medicines have the same effect on rehabilitation of symptoms (they might differ in the time to take effect and the dose to use). However, the physician needs to familiarize himself with four medicines. The side effect of the medicines includes drowsiness (phenothiazines), extrapyramidal side effects (piperazine), etc. How does the medicine take effect on rehabilitation is still needs to be studied. Still, several theories have already been advocated: one of those theories announces that neuroleptic drugs reduce the arousal of the central nervous system (CNS) [32].

4.2 Nonpharmacological therapy of schizophrenia

As this article has already talked about before, without antipsychotic medicine, the rehabilitation program of schizophrenia can't be processed, but it doesn't mean that nonpharmacological therapy (NPT) is useless. In fact, nonpharmacological therapy takes an auxiliary effect on the treatment of schizophrenia. The main targets of NPT are targeting symptoms, preventing relapse, and increasing adaptive function [35]. Usually, psychotherapeutic approaches can be divided into 4 categories: Cognitive Remediation Therapy (CRT), Cognitive Behavioral Therapy (CBT), Transcranial Magnetic Stimulation (TMS), and Transcranial Direct Current Stimulation (TDCS). In the following part, we will briefly introduce those nonpharmacological treatments.

1) Traditional nonpharmacological therapy

Cognitive remediation therapy (CRT) is a behavioral training-based intervention that aims to improve cognitive functioning and the Impact of Non-pharmacological Interventions on Brain Structure and Function in schizophrenia behavior. Cognitive remediation therapy (CRT) is a behavioral training-based intervention that improves cognitive functioning and behaviors. It aims to teach skills and tactics to enhance cognition, hoping that improvements in cognitive domains will enrich community functioning. Studies have already proved that CRT can improve the abilities in most cognitive domains except for memories and visual learning. [42] Most CRT treatment approaches separately target neurocognitive or sociocognitive factors. Still, some cognitive therapies, such as cognitive enhancement therapy (CET), utilize an integrated approach of both neurocognitive and social cognitive factors for maximal treatment outcomes.

Cognitive behavioral therapy (CBT) is a psychological intervention that aims to improve mental health by establishing links between thoughts, emotions, and behavior to help with emotional regulation and coping strategies. CBT can reduce the severely positive symptoms of schizophrenia and comorbid affect states and reduce potential relapse. Through the process of CBT, the patient can develop the strategies to release their stress and reestablish cognization.

Transcranial magnetic stimulation (TMS) is a neuromodulation that provides a new frontier in potential effective treatment options for schizophrenia [43]. By using the alternating magnetic field to stimulus, the generate current in the cortex. When the frequency of TMS is at a low level, the treatment will take an inhibitory effect according to the GABAergic effects and long-term neuronal depression [43]. While when the frequency of the pulse is low, TMS will take an excitatory effect through the glutaminergic effect. Pulses that are delivered in single, pair or series, called a train. TMS delivered in a train is referred to as repetitive TMS (rTMS). No anesthesia is required when administering TMS, and patients can usually leave immediately following their session.

Transcranial direct-current stimulus (TDCS) is neuromodulation that uses constant, low direct current via electrodes [42]. According to the studies, TDCS might be a potential treatment to alter frontal cortical activity and enhance pro-cognitive effects since TDCS of the medial frontal cortex was associated with increased activation of this region and also positively associated with the consolidation of working memory performance 24 h post-stimulation [44].

2) Genetic treatment

All the therapy that we discussed before are targeting to reduce the positive and negative symptoms of schizophrenia, or in some way, relieve the acute symptoms. None of them can cure schizophrenia completely. Due to the development of genetic techniques, we are looking forward to curing schizophrenia at the genetic level. Clustered regularly interspaced palindromic repeats (CRISPR) is a gene-editing technology causing a major upheaval in biomedical research. It makes it possible to correct errors in the genome and turn on or off genes in cells and organisms quickly, cheaply, and with relative ease. CRISPR/Cas9 is a gene-editing technology that involves two essential components: a guide RNA to match the desired target gene and Cas9 (CRISPR-associated protein 9)—an endonuclease that causes a double-stranded DNA break, allowing modifications to the genome [45]. As we have already discussed, NRG1 and GABA have a great relation with affecting schizophrenia. Applying the CRISPR technique in the therapy of schizophrenia still needs to be probed and will be our future learning target.

5. Conclusion

Schizophrenia is a mental disease that influences 0.5-1.0% population world-widely. Patients are mostly distributed between the age of 18 to 31. The manifestation of schizophrenia includes 2 main categories: positive symptoms and negative symptoms. Positive symptoms mainly refer to hallucination and delusion, which means alienation occurs at the perception of patients. Negative symptoms also refer to disorders in emotion. The patient with schizophrenia always has deficits in anticipatory pleasure, especially in abstract anticipatory pleasure. Infection of schizophrenia always causes a giant mental injury to the patients; this injury usually causes by positive symptoms like persecutory delusion. This mental injury might turn into self-destructing and suicide. Also, negative symptoms will reduce the social ability of patients, which causes marginalization. Studies have shown that PTSD related to childhood experience might be a psychotic inducement to schizophrenia. However, according to the research results showing a high positive correlation of prevalence for offspring infection and parents' infection, scholars believe that gene is another significant inducement of schizophrenia. Many modulations have been supposed that hypothesis mainly focuses on how genes influence neurotic receptors, cause abnormal development of the human brain, and finally cause schizophrenia.

NRG1 is a candidate gene that has been proved to be related to the infection of schizophrenia. It is a tropical factor that might contain an EGF-domain, which plays an essential role in activating the ErbB receptor tyrosine kinases. The negative influence of the NRG1-ErbB signal in the development of the brain is considered to have the same effect as the "abnormal neural development" model of schizophrenia.

Current popular therapy of schizophrenia is mainly based on antipsychotic medicine. This kind of therapy aims to reduce the severe symptoms of schizophrenia and fix the abnormal activity in the neuron system. Nonpharmacological like CRT and CBT is usually used to make patients get basic information about their illness and stick to the therapy of antipsychotic treatment. Researchers announce that some categories of nonpharmacological treatment can be useful to restables personalities of schizophrenia patients and make them get back to society. Yet both pharmacological and nonpharmacological treatment can only anises the symptoms but can't cure them. We are looking at a genetic revision technique, CRISPR, to improve this situation in the future. We believe the development in this area can solve this problem at the genetic level.

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