

How the Gene NRG1, Erbb4, DAOA, and DISC1 Can Affect the Schizophrenia

Jiayi Zang

School of Biological Sciences Shenzhen MSU-BIT University Shenzhen China

1120200215@smbu.edu.cn

Abstract. Schizophrenia is a mental disease that affects many people. Up to now, it is still difficult to cure. So, it is important to find the causes of this disease. Genes play an important role in the many cause of schizophrenia. Many researchers have found that the genes NRG1, Erbb4, DAOA, and DISC1 can cause schizophrenia by affecting some structures of the nervous system and directly or indirectly affecting the release of neurotransmitters. Of course, each gene may have a specific pathway leading to the disease. Different genes can also interact with other genes to affect diseases, such as gene NRG1 and Erbb4, gene DAOA and DISC1. This paper summarizes some recent experiments to find the relationship between genes and schizophrenia. Some of the causes of schizophrenia summarized in this paper are important for the development of drugs to treat the disease.

Keywords: Schizophrenia, NRG1, Erbb4, DAOA, DISC1.

1. Introduction

As we all know schizophrenia is a mental disease. There are about 1% of people in the world, are affected by schizophrenia. It is very difficult to cure this disease and the reason for this disease is unclear. Although some patients with schizophrenia can get better with medication or psychotherapy, they are still not completely cured. And the current psychotherapeutic drugs can only work for some people, not all the people can use the drugs. Psychotherapeutic drugs also have side effects, such as loss of emotional control, weight gain, and difficulty controlling blood sugar levels [1]. For this reason, many researchers began to do a lot of research about the cause of schizophrenia to find a better way to cure this disease.

There are many reasons that can cause schizophrenia. However, genetics is a very important reason for schizophrenia. Many researchers found that genetic mutations or gene deletion can cause this disease. Genetic mutations and gene deletion can cause structural changes in the brain and affect the release and absorption of substances such as neurotransmitters. There are many genes that can influence schizophrenia, such as NRG1, Erbb4, DAOA, and DISC1. The neuregulin 1 (NRG1) can affect synapse number and synaptic plasticity. Gene Erbb4 is the receptor of NRG1. The Erbb4 and NRG1 can control the development of both excitatory and inhibitory cortical circuits. And the gene Erbb4 is also a very important gene, which can affect the signaling pathways. Gene DAOA is the D-amino acid oxidase activator gene, which was called gene G72. Gene DAOA is related to structures such as the hippocampus. And the hippocampus plays an important role in information processing. The next gene is the gene DISC1. In some research, the mRNA DISC1, which was found in patients with schizophrenia is lower than in other people. And the compound DISC1 is also important to schizophrenia.

This paper aims to summarize the function of the four genes (NRG1, Erbb4, DAOA, and DISC1) in the treatment of schizophrenia. How do these genes influence the disease? And a combination of multiple genes.

2. The background of schizophrenia

Schizophrenia is a complex mental disease, and it has a high probability of being inherited. For schizophrenia, there is no clear reason. Schizophrenia affects nearly 1% of the world's population [2].

It occurs mostly in young adults. It also runs in families. Environmental factors, disease, stress, and psychological factors may cause schizophrenia. It can cause perceptual disorders, thought disorders, emotional disorders, volitional and behavioral disorders, and cognitive dysfunction. Schizophrenia is now mainly treated with medication and psychotherapy. The disease can cause cognitive deterioration. But the medicine cannot improve cognitive problems. Now many hospitals use a combination of medicine and psychotherapy to treat schizophrenia. This is a good way to treat it, but it also cannot make the patient completely better. So, it is very important to find the reason for schizophrenia. Many researchers have told that genetics is a very important reason for this disease. The following will introduce the gene affecting.

3. How the NRG1 influence the schizophrenia

The neuregulin 1 is the full name of gene NRG1. This gene is located on chromosome 8. The gene type is protein-coding. This gene produces a membrane glycoprotein that mediates cell-cell signaling and is important for the growth and development of numerous organ systems. Gene NRG1 plays important role in the development of motor and sensory neurons and it also can affect synapse number and synaptic plasticity.

The NRG1 plays an important role in neuronal migration and regulation of synaptic plasticity [3]. Both excitatory and inhibitory cortical circuits are controlled by NRG1 and its receptor ErbB4 [4]. As a result, if the gene NRG1 affects the cortex, mental disease may result.

And from the research, the high-level NRG1 can impair the dendritic spines. Researchers studied ctoNRG1 animals, compound mice of CaMK2-tTA, and TRE-NRG1 mice to see if higher levels of NRG1 harm dendritic spines in vivo [5]. By comparing the different groups' mice's levels of NRG1 and the spine density, can be concluded that high levels of NRG1 can reduce the dendritic spines density. This work also revealed that mice overexpressing NRG1 in neurons have lower dendritic spine density in the prefrontal cortex and hippocampus. Dendritic spines are the spine-like protrusions on dendritic branches and are the main sites for the formation of synapses between neurons. NRG1 can affect the synapses by affecting the dendritic spines.

Cortical disinhibition is a common feature of several psychiatric disorders, including schizophrenia. The cerebral cortex is another name for the cortex. The gray matter of the two hemispheres of the brain is covered by the cerebral cortex. It is the building block for advanced brain functions. It is composed of neurons, nerve fibers, and glia. The inhibitory function of the cortex can protect the brain from the damage caused by overuse. So, if cortical disinhibition occurs, the brain may damage. In the experiment, the researchers compared the gtoNRG1 mice with overexpression of NRG1 in GABAergic interneurons with the normal mice. gtoNRG1 mice show the cortical disinhibition in a cell, synaptic, and the neural network [6]. And the experiment also proved that the gtoNRG1 mice were hyperactive in the open-field test, which proves that the gtoNrg mice had abnormal dopamine levels. Too much dopamine can lead to hyperarousal. And the long-term high levels of dopamine can cause irreversible damage to the nerve cells, which may lead to schizophrenia.

Through these two experiments, the results have shown that the high level of gene NRG1 can change the number of synaptic and cause cortical disinhibition. The synaptic and cortex are important for the nervous system. So, it could be argued that gene NRG1 can cause schizophrenia by affecting synapses and causing cortical disinhibition.

4. How the ErbB4 influence the schizophrenia

ErbB2 receptor tyrosine kinase 4 is the full name of ErbB4. Gene ErbB4 is located on chromosome 2. The gene type is protein-coding. It is highly expressed in the brain. This gene is a member of the Tyr protein kinase family and the epidermal growth factor receptor subfamily. In the nervous system, ErbB4 mainly acts as the receptor of NRG1 in the signaling pathway. ErbB4 signaling is involved in

a variety of neurodevelopmental processes, including neurogenesis, synapse growth, and circuit construction and function.

The research found that the gene *ErbB4* is also a risk gene for schizophrenia. Delete the gene *ErbB4* may affect the synaptic and certain functions of the amygdala. It can also affect the chandelier cells to cause schizophrenia.

ErbB4 is strongly expressed in GABAergic intercalated cell clusters (ITCs) in the amygdala. The amygdala is the gray matter nuclei inside the brain that are involved in emotion, behavior, and neurobehavioral. In the experiments, researchers generated an ITC-targeted *ErbB4* knockout and controls to do this [7]. By comparing the experimental data of the two groups, it is found that *ErbB4* deletion from mpITCs disrupted the balance between excitation and inhibition in the amygdala and affected learning mechanisms. This is because the knockout affects the synaptic structure in the amygdala. NMDA receptor-mediated synaptic transmission is inhibited, resulting in long-term synaptic damage.

Chandelier cells (also known as axonal cells) are a subtype of GABAergic interneurons that target the first segment of axons, which is where pyramidal neurons initiate action potentials. In the experiment, the mice were obtained by hybridization with different types of mice. The gene *ErbB4* is knocked out in chandelier cells of the medial prefrontal cortex in the acquired animals [8]. Using these mice and controls to conduct the experiment and check the chandelier cells content. The mice which are selectively knocked out of the *ErbB4* have a low level of chandelier cells. Then they did a lot of tests on the mice and found that the mice which had been knocked out of the *ErbB4* had schizophrenia. Hyperactivity, reduced PPI, and impaired working memory and social novelty cognition are the specific symptoms. Through these two experiments, the researchers found that if the gene *ErbB4* was knocked out or missing can affect the synaptic structure in the amygdala and the number of chandelier cells in the medial prefrontal cortex. We know the amygdala and cortex are an all-important part of the nervous system. In the experiments mice that were knocked out of the *ErbB4* all get schizophrenia. To conclude that schizophrenia is associated with *ErbB4*.

5. How the *ErbB4* and NRG1 influence the schizophrenia

The researches and experiments have found that the function of genes NRG1 and *ErbB4*, and how the genes NRG1 and *ErbB4* cause schizophrenia by affecting the nervous system have been known. The *ErbB4* is the receptor of NRG1. So NRG1 and *ErbB4* may have some interaction in schizophrenia.

NRG1-*ErbB4* signaling regulates various neurodevelopmental processes, particularly migration, synapse formation, and myelination of cortical interneurons. Also involved in multiple processes of cortical circuitry transmission. So, the NRG1-*ErbB4* signaling is thought to be an important factor in schizophrenia. In the experiments, researchers use the CRD-NRG1 transgenic mice and controls to do μ CT Scans and biochemical analysis and found that the mice have enlarged ventricles and hyperactivity [9]. These are also manifestations of schizophrenia. This is mainly caused by signal channel overexpression.

The research found that the NRG1-*ErbB4* signaling is also involved in multiple processes of cortical circuitry transmission. So, their roles in assembling the GABAergic circuit are very important. The experiment showed that the cortex of mice mutated in the gene *ErbB4* has lower GABAergic interneurons. This conclusion also supports that the gene *ErbB4* plays a role in neuronal migration. As quantified by PSD-95 and GluA1-positive puncta and miniature excitatory postsynaptic potential (mEPSC) frequency, the NRG1-*ErbB4* signaling promotes the formation and maturation of GABAergic excitatory synapses. So, found that the NRG1-*ErbB4* signaling can lead to schizophrenia by affecting the GABAergic neurons [10].

In addition, Multiple studies have shown that the Neuregulin-1- (NRG1-) *ErBb4* signaling pathway plays a crucial role in the development of cortical inhibitory neurons. Application of NRG1 to cortical neuronal cultures results in increased dendritic growth and excitatory synaptogenesis on

inhibitory neurons, while inhibitory neuron-specific ErbB4 knockout mice show reduced excitatory synaptogenesis on cortical inhibitory neurons.

6. How the DAOA influence the schizophrenia

D-amino acid oxidase activator is the full name of DAOA. DAOA is located on chromosome 13. This gene codes for a protein that may operate as an activator of D-amino acid oxidase, an enzyme that degrades the gliotransmitter D-serine, which is a potent activator of glutamate receptors of the N-methyl-D-aspartate (NMDA) type. DAOA is mainly expressed in the amygdala and caudate nucleus. The caudate nucleus is an arcuate rod-shaped mass of gray matter, all attached to the vicinity of the lateral ventricle. And it is close to the amygdala. If it was broken, may cause decreased muscle tension, and too much movement too fast. So, this is should that the gene can cause schizophrenia by affecting the neural structures or the neurotransmitter.

In a large number of studies, d-amino acids, especially D-serine, be associated with brain and nervous system diseases. Neurotransmission, learning, and memory activities are among the recognized brain functions of d-amino acids, which are mediated via N-methyl-d-aspartate glutamate receptors (NMDARs) Genes related to d-amino acid metabolism can directly affect the content of d-amino acid. DAOA is an important gene related to d-amino acid metabolism. So, in many experiments, dysfunction of the NMDARs has been shown to contribute to schizophrenia. This is mainly due to the effect of the NMDARs dysfunction on D-serine content. The researchers came to their conclusion by comparing D-serine levels in the brains of schizophrenics after death with normal people [11]. Studies have shown that d-serine levels and the d/l-serine ratio in the cerebrospinal fluid of patients with schizophrenia are reduced by 25%. Including decreased D-serine levels in the serum. So, it was found that the gene DAOA could affect the content of D-serine by affecting the NMDARs. Low D-serine levels can cause schizophrenia.

In DAOA, two frequent SNPs are rs746187 and rs1421292. In the context of fMRI findings in other tasks, such as the verbal working memory task, DAOA risk alterations were found to positively effect hippocampus and parahippocampal activation in healthy persons. In bearers of the rs3918342 and rs1421292 risk alleles, hippocampus and parahippocampal activity is dramatically diminished. In first-episode schizophrenia, variation in DAOA rs2391191 is linked to decreased FA in the corpus callosum, implying compromised white matter integrity [12].

Some researchers found that, pLG72 the product of gene DAOA can interact with superoxide dismutase 1 (SOD1), which results in SOD1 aggregation. This can lead to neurodegenerative diseases, such as schizophrenia. Recultured pLG72 cells were compared with normal cells. The interaction between pLG72 and SOD1 was detected by CoralHue fluorescence tracing [13]. It has been found that pLG72 can cause SOD1 aggregation and reduce the content of SPD1. The decrease of SOD1 content may damage the neurons, which leads to neurodegenerative disease.

So, the researchers have shown that the DAOA can cause schizophrenia by affecting the NMDARs, the hippocampus, and the SOD1.

7. How does the gene DISC1 influence schizophrenia

7.1. The gene DISC1 can affect the transport of Ca^{2+}

The gene DISC1 is located on chromosome 1. This gene produces a protein that has numerous coiled-coil patterns in the nucleus, cytoplasm, and mitochondria. The gene also encodes a scaffold protein. Through its interactions with other proteins, the protein plays a role in synaptic formation and cortical development. In a t (1; 11) (q42.1; q14.3) translocation, the gene may be disrupted, resulting in schizophrenia. The dentate gyrus of the hippocampus is highly expressed. White matter cells and temporal and parahippocampal cortices are also affected. So, the gene may cause schizophrenia by affecting the neural structures such as the hippocampus, cortex, or the white matter.

Some researchers should that in the patients with schizophrenia have found lower DISC1mRNA. In the experiment, the researchers use 32 patients with schizophrenia and 24 healthy controls to do the research. They used peripheral blood from all subjects to examine DISC1 mRNA expression. Also used the Positive and Negative Syndrome Scale (PANSS), Hamilton Rating Scale for Depression (HAMD), Brief Psychiatric Rating Scale (BPRS) and Scale for the Assessment of Negative Symptoms (SANS) scales to evaluate patients with schizophrenia. And use the HAMD scale to assess the healthy subjects [14]. The level of DISC1 mRNA in schizophrenia patients is shown to be considerably lower than in healthy persons. Also, have concluded that the patients with schizophrenia who have a lower DISC1mRNA level have the more obvious symptoms such as depression.

DISC1 is involved in or regulates Ca^{2+} in adult central neurons. DISC1 plays a tethering role in the transport of RNA particles containing Ca^{2+} channel subunit RNAs, and in the transport of mitochondria to dendrites and axons [15]. The researchers have found that the DISC1 promotes mitochondrial Ca^{2+} -sensitive anterograde motility (1A), and as intracellular Ca^{2+} rises, DISC1 dissociates from the complex, allowing syntrophin (SNPH) and Miro1 to interact to anchor mitochondria in place (Figure 1A). And the DISC1 regulates Ca^{2+} transfer from the ER to mitochondria via mitochondrial membrane (MAM). (Figure 2A) So it may be concluded that the gene can affect the release of neurotransmitters by affecting the transport of Ca^{2+} in the mitochondrial membrane. So, from the research, it is concluded that the gene DISC1 can cause schizophrenia by affecting the mRNA DISC1 level and transport of Ca^{2+} , suggesting that the gene DISC1 has a link with schizophrenia. So, from the research, it is concluded that the gene DISC1 can cause schizophrenia by affecting the mRNA DISC1 level and transport of Ca^{2+} .

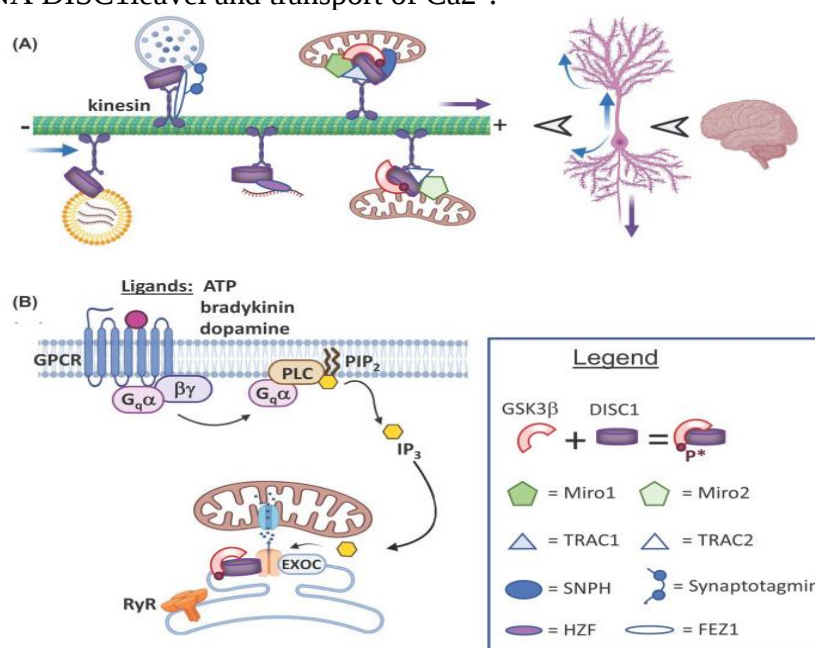


Figure 1. In adult central neurons, DISC1 regulates cargo transport along microtubules and Ca^{2+} transfer from the ER to mitochondria at the MAM [15]. A) DISC1 binds with the driver protein motor complex to regulate access to dendrites or nerve endings. B) DISC1 binds to IP3Rs in the MAM to reduce the amount of Ca^{2+} transferred to the mitochondria

7.2. The DISC1 influence the NRG1-ErbB4 signaling pathway

In the mature cortex, DISC1 regulates NRG1-ErbB4 signaling and excitatory-inhibitory synapse development. Postsynaptic density protein-95 interacts with both DISC1 and ErbB4 (PSD95). DISC1 may affect NRG1-ErbB4 signaling by associating with PSD95 scaffolds in interneurons. First, knock out the gene DISC1 to see if it affects NRG1-induced ErbB4 activation in vitro. Phosphorylated ErbB4 (pErbB4) immunoreactivity as an indicator of NRG1-ErbB4 signaling. The experimental data can show that DISC1 knockdown enhances the activation of ErbB4 by NRG1 [16]. Signaling pathway

NRG1-ErbB4 plays an important role in the development of the nervous system. So DISC1 can cause schizophrenia by affecting NRG1-ErbB4 signaling.

8. How the DAOA and DISC1 influence the schizophrenia

A recent study found that the genes DAOA and DISC1 may influence visual learning in schizophrenics. In the experiment, the researchers classified genes for DISC1Ser704Cys and DAOA24SNPs in patients with schizophrenia. And use the Visual Reproduction II to assess the visual learning. Finally, it can be concluded that the genetic defect in gene DAOA and DISC1 can reduce the efficiency of visuals through experimental data [17]. Lack of visual learning is characterized by a lack of concentration and sensitivity to what is being seen. There are also manifestations of schizophrenia. So, it proves that the genetic defect in gene DAOA and DISC1 may cause schizophrenia.

Table 1. A comparison of the four genes

Gene	Function	Location	Relation with Disease
NRG1	membrane glycoprotein that mediates cell-cell signaling	Chromosome 8	Affect dendritic spines and cortical disinhibition
ErbB4	as the receptor of NRG1 in the signaling pathway	Chromosome2	Affect the amygdala and chandelier cells
DAOA	an activator of D-amino acid oxidase	Chromosome13	Affect the hippocampus, SOD1 and N-methyl-d-aspartate glutamate receptors (NMDARs)
DISC1	cortical development and synaptic growth	Chromosome1	Affect the Ca ²⁺ in adult central neurons

9. Conclusion

Genes can cause schizophrenia by affecting important structures in the nervous system, such as the synapses, cortex, hippocampus, etc. But the four genes NRG1, ErbB4, DAOA (G72), and DISC1 have different effects on disease. The high level of the NRG1 can affect the synapses by impairing the dendritic spines. And can also affect the cortical disinhibition to make high levels of dopamine, which may damage the nerve cells. The study found that when the gene ErbB4 is knocked out it may affect the synaptic structure of the amygdala and reduced the number of axon cells. ErbB4 as a receptor of the NRG1, the NRG1-ErbB4 signaling pathway can cause schizophrenia by affecting the process of neural development or transmission of electrical signals. The DAOA can affect the N-methyl-d-aspartate glutamate receptors (NMDARs) to reduce the D-serine content or affect the number of the SOD1 to damage the nerve cells. It can also affect the hippocampus. The gene DISC1 can affect schizophrenia by regulating Ca²⁺ levels in central neurons. The Ca²⁺ can affect the release of neurotransmitters. The gene DAOA and DISC1 work together with the visual learning system of schizophrenics. And the low level of DISC1 can affect the NRG1-ErbB4 signaling. But the study still has limitations. A lot of the data came from experiments on mice, which is a difference with humans, so the data may not accurate. Schizophrenia may be better treated by studying its gene cause.

References

- [1] Lago SG, Bahn S. The druggable schizophrenia genome: from repurposing opportunities to unexplored drug targets. NPJ Genom Med. 2022 Mar 25; 7 (1): 25.

- [2] Cheng P, Zhang R, Shan S, Yuan B, Chen J, Qiu Z, Du Y. Novel IL1RAP mutation associated with schizophrenia interferes with neuronal growth and related NF- κ B signal pathways. *Neurosci Lett*. 2022 Apr 1; 775: 136533.
- [3] Yang H, Pan W, Xiao W, Yang M, Xu J, Li J, Zhang X. Antipsychotic drugs increase Neuregulin1 β 1 serum levels in first-episode drug-naïve patients and chronic schizophrenia with suggestions for improving the treatment of psychotic symptoms. *BMC Psychiatry*. 2022 Mar 25; 22 (1): 217.
- [4] Navarro-Gonzalez C, Carceller H, Benito Vicente M, Serra I, Navarrete M, Domínguez-Canterla Y, Rodríguez-Prieto Á, González-Manteiga A, Fazzari P. NRG1 haploinsufficiency alters inhibitory cortical circuits. *Neurobiol Dis*. 2021 Sep; 157: 105442.
- [5] Chen P, Jing H, Xiong M, Zhang Q, Lin D, Ren D, Wang S, Yin D, Chen Y, Zhou T, Li B, Fei E, Pan BX. Spine impairment in mice high-expressing neuregulin 1 due to LIMK1 activation. *Cell Death Dis*. 2021 Apr 14; 12 (4): 403.
- [6] Wang YY, Zhao B, Wu MM, Zheng XL, Lin L, Yin DM. Overexpression of neuregulin 1 in GABAergic interneurons results in reversible cortical disinhibition. *Nat Commun*. 2021 Jan 12; 12 (1): 278.
- [7] Asede D, Okoh J, Ali S, Doddapaneni D, Bolton MM. Deletion of Erbb4 Disrupts Synaptic Transmission and Long-Term Potentiation of Thalamic Input to Amygdalar Medial Paracapsular Intercalated Cells. *Front Synaptic Neurosci*. 2021 Jul 28; 13: 697110.
- [8] Yang JM, Shen CJ, Chen XJ, Kong Y, Liu YS, Li XW, Chen Z, Gao TM, Li XM. Erbb4 Deficits in Chandelier Cells of the Medial Prefrontal Cortex Confer Cognitive Dysfunctions: Implications for Schizophrenia. *Cereb Cortex*. 2019 Sep 13; 29 (10): 4334-4346.
- [9] Götze T, Soto-Bernardini MC, Zhang M, Mießner H, Linhoff L, Brzózka MM, Velanac V, Dullin C, Ramos-Gomes F, Peng M, Hussein H, Schifferdecker E, Fledrich R, Sereda MW, Willig K, Alves F, Rossner MJ, Nave KA, Zhang W, Schwab MH. Hyperactivity is a Core Endophenotype of Elevated Neuregulin-1 Signaling in Embryonic Glutamatergic Networks. *Schizophr Bull*. 2021 Aug 21; 47 (5): 1409-1420.
- [10] Mei L, Nave KA. Neuregulin-ERBB signaling in the nervous system and neuropsychiatric diseases. *Neuron*. 2014 Jul 2; 83 (1): 27-49.
- [11] Cheng YJ, Lin CH, Lane HY. d-Amino Acids and pLG72 in Alzheimer's Disease and Schizophrenia. *Int J Mol Sci*. 2021 Oct 9; 22 (20): 10917.
- [12] Lin Z, Long Y, Wu Z, Xiang Z, Ju Y, Liu Z. Associations between brain abnormalities and common genetic variants for schizophrenia: a narrative review of structural and functional neuroimaging findings. *Ann Palliat Med*. 2021 Sep; 10 (9): 10031-10052.
- [13] Wang M, Saw HP, Cui FF, Lin SY, Chang HT, Chiu CD. pLG72 induces superoxide radicals via interaction and aggregation with SOD1. *Free Radic Res*. 2018 Sep; 52 (9): 970-976.
- [14] Chen YM, Lin CH, Lane HY. Distinctively lower DISC1 mRNA levels in patients with schizophrenia, especially in those with higher positive, negative, and depressive symptoms. *Pharmacol Biochem Behav*. 2022 Feb; 213: 173335.
- [15] Rittenhouse AR, Ortiz-Miranda S, Jurczyk A. Mutations in DISC1 alter IP3R and voltage-gated Ca²⁺channel functioning, implications for major mental illness. *Neuronal Signal*. 2021 Dec 7; 5 (4): NS20180122.
- [16] Seshadri S, Faust T, Ishizuka K, Delevich K, Chung Y, Kim SH, Cowles M, Niwa M, Jaaro-Peled H, Tomoda T, Lai C, Anton ES, Li B, Sawa A. Interneuronal DISC1 regulates NRG1-ErbB4 signalling and excitatory-inhibitory synapse formation in the mature cortex. *Nat Commun*. 2015 Dec 11; 6: 10118.
- [17] Chang JP, Huang KH, Lin CH, Lane HY. Genetic Effects of DISC1 and G72 (DAOA) on Visual Learning of Patients with Schizophrenia. *Neuropsychiatr Dis Treat*. 2020 Mar 20; 16: 771-780.