Lost and Found: Deletion of Zdhhc8 gene is associated with schizophrenia

Kristina Karapetyan
Department of Biology
Lake Forest College
Lake Forest, Illinois 60045

Schizophrenia disorder might develop as a result of various genetic factors, and one of them is a gene deletion. The researchers have demonstrated that one of the genes that gets deleted in the DiGeorge syndrome contributes to the schizophrenia phenotype. This gene is Zdhhc8.

A restless person with insane eyes who talks to himself has hallucinations and hears voices. That's a trivial depiction of someone who is suffering from schizophrenia. However, this disorder has many manifestations: A schizophrenic person might be completely emotionless, show cognitive dysfunctions, and barely move. Symptoms that are exhibited by schizophrenic individuals depend on various factors, and one of these factors is genetics. Schizophrenia research recently has identified multiple genes which are associated with a risk of getting schizophrenia: GRIN2A gene was linked to schizophrenia in 2013, GRIA1 in 2014, and C4 genes in 2016 (Paoletti et al., 2013; Barkus et al., 2014; Sekar et al., 2016). All of these discoveries demonstrate that schizophrenia is a complex disorder, which involves multiple risk factors, and that each risk factor contributes to a separate facet of schizophrenia. These studies suggest that some people have a higher chance of developing schizophrenia and one of the high risk groups are children with a 22q11.2 deletion.

22q11.2 deletion, also known as DiGeorge syndrome, is characterized by such features as immune deficiency, hypoparathyroidism, cognitive dysfunctions and emotional difficulties (Swillen et al., 2000). Interestingly, some studies have found links between 22q11.2 deletion and schizophrenia. For example, Karayiorgou and colleagues examined schizophrenia patients and found that two patients out of a hundred carried 22q11.2 deletions (Karayiorgou et al.,1995). Such a finding might appear minor; however, another study conducted by Pulver and colleagues demonstrated that about 30% of children with 22q11.2 deletion develop schizophrenia during adulthood (Pulver et al., 1994). The question that was posed by the scientists was whether the entire deleted region leads to the development of schizophrenia or whether among these genes there is one that most contributes to the development of schizophrenia. Mukai and his colleagues decided to undertake this task and test whether the deletion of a single gene that is located in 22q11.2 region would lead to the development of schizophrenia features and symptoms (Mukai et al., 2015). This gene was Zdhhc8.

Zdhhc8 has various significant functions; one of these critical functions is palmitoyltransferase production. Palmitoyltransferase is an enzyme that is involved in the protein palmitoylation process. This process is characterized by the formation of a thioester bond between a cysteine and a saturated fatty acid, also known as palmitate lipid (Guan et al., 2011). Protein palmitoylation might modify peripheral and integral membrane proteins permanently as well as temporarily, which is a unique feature for lipid modification of proteins (Guan et al., 2011). Addition of palmitate to a protein impacts the protein-lipid interaction which in turn affects the regulation of protein trafficking and the regulation of various membrane and cytosolic proteins, especially in neurons. Since Zdhhc8 is responsible for this crucial mechanism, Makai and colleagues decided to test how deletion of this particular gene would affect mice phenotype and whether it would be similar to the schizophrenia phenotype.

The researchers hypothesized that after the deletion of Zdhhc8 they should observe changes on molecular, cellular and behavioral levels, which would resemble features seen in schizophrenia. The study had multiple goals and some of them included assessing protein palmitoylation in vitro, examining axonal growth and branching, and lastly, evaluating connectivity between the hippocampus and medial prefrontal cortex and how that impacts the working memory.

To determine how protein palmitoylation was impacted by the Zdhhc8 gene deletion, researchers extracted proteins from the Zdhhc8−/− and wild-type mice embryonic cortical neurons. They added various substrates to test palmitoylation and their analysis showed that, compared to wild-type neurons, palmitoylation level in Zdhhc8 knockout neurons was reduced for some of the substrates such as PSD95 and GRIP 1, but not for others, for example SNAP25 and Fyn. The strongest reduction of palmitoylation in Zdhhc8 knockout neurons was observed for Cdc42 and Rac1 substrates, which are responsible for the regulation of the axonal development and cell polarity in neurons. In Zdhhc8−/− neurons, palmitoylation of Cdc42 was reduced by 33% and palmitoylation of Rac1 was reduced by 38%.

Since palmitoylation of Cdc42 and Rac1 was reduced as a result of Zdhhc8 deletion and these proteins influence morphology, the researchers made a logical assumption that this would lead to some changes on the cellular level. This assumption was supported by their findings. The wild-type mice had neurons with normal polarity, and most of them had a single axon and multiple dendrites while Zdhhc8 knockout mice had a decreased number of neurons with a single axon. Zdhhc8+/− and Zdhhc8−/− mice exhibited a reduction in primary axon length compared to the wild-type mice. Also, Zdhhc8 deletion led to a decrease in the number of branch points in the Zdhhc8 knockout mice compared to the wild-type mice. These alterations on the cellular level translated into behavioral changes.

One of the most intriguing questions that Makai and colleagues asked was whether the deletion of Zdhhc8 disrupts the connectivity between the hippocampus and the medial prefrontal cortex and how it affects working memory (WM). To assess working memory they employed the T-maze paradigm. They observed how many days it will take for the Zdhhc8 deficient mice compared to the wild-type mice to reach a criterion performance on the T-maze task. In order to examine the connectivity between the hippocampus and the medial prefrontal cortex when the mice were performing the T maze task, the researchers used the theta-frequency coherence, which is one of the measurements of connectivity between brain regions. Behaviorally, the knockout mice took significantly longer than the wild-type mice to reach criterion performance on the T-maze task, which demonstrates impairment of spatial WM in the Zdhhc8 knockout mice. Interestingly, the brain connectivity analysis showed lower theta-frequency coherence between the hippocampus and the medial prefrontal cortex during the T maze task. Therefore, such a finding demonstrates that Zdhhc8 knockout mice exhibit some deficits in connectivity between the hippocampus and the medial prefrontal cortex, which might contribute to the impaired working memory performance. Impairment in the working memory is one of the known cognitive symptoms of schizophrenia. Therefore this study illustrates that the deletion of the single gene leads to the development of some schizophrenia features.

This study is very important to the schizophrenia research field because it made a few remarkable findings. It investigated the link between 22q11.2 deletion and schizophrenia and demonstrated that one of the deleted genes in the DiGeorge syndrome also contributes to the development of schizophrenia symptoms. Zdhhc8 gene deletion contributes to the alterations on the cellular, anatomical, and behavioral levels which results in schizophrenia features (See Figure 1). This study is significant since it shows that while studying one disorder we can learn something new about causes and mechanisms of a different disorder.

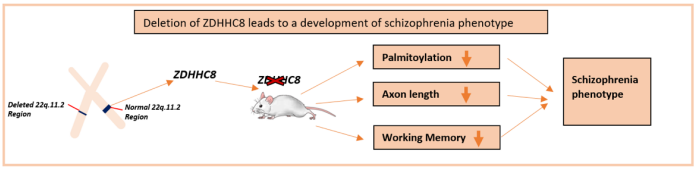

Figure 1. Deletion of the Zdhhc8 gene leads to the schizophrenia phenotype

Note: Eukaryon is published by students at Lake Forest College, who are solely responsible for its content. The views expressed in Eukaryon do not necessarily reflect those of the College.

References

Barkus C, Sanderson DJ, Walton ME, et al. (2014) What causes aberrant salience in schizophrenia? A role for impaired short-term habituation and the GluA1 AMPA receptor. Mol Psychiatry 19: 1060–1070.

Guan, X., & Fierke, C. A. (2011). Understanding protein palmitoylation: Biological significance and enzymology. Science China Chemistry,54(12), 1888-1897. doi:10.1007/s11426-011-4428-2

Karayiorgou, M., Morris, M. A., Morrow, B., Shprintzen, R. J., Goldberg, R., Borrow, J., . . . Lasseter, V. K. (1995). Schizophrenia susceptibility associated with interstitial deletions of chromosome 22q11. Proceedings of the National Academy of Sciences,92(17), 7612-7616. doi:10.1073/pnas.92.17.7612

Mukai, J., Tamura, M., Fénelon, K., Rosen, A., Spellman, T., Kang, R., . . . Gogos, J. (2015). Molecular Substrates of Altered Axonal Growth and Brain Connectivity in a Mouse Model of Schizophrenia. Neuron,86(3), 680-695. doi:10.1016/j.neuron.2015.04.003

Paoletti P, Bellone C and Zhou Q (2013) NMDA receptor subunit diversity: Impact on receptor properties, synaptic plasticity and disease. Nat Rev Neurosci 14: 383–400

Perlstein, W. M., Carter, C. S., Noll, D. C., & Cohen, J. D. (2001). Relation of Prefrontal Cortex Dysfunction to Working Memory and Symptoms in Schizophrenia. American Journal of Psychiatry,158(7), 1105-1113. doi:10.1176/appi.ajp.158.7.1105

Pulver, A.E., Nestadt, G., Goldberg, R., Shprintzen, R.J., Lamacz, M., Wolyniec, P.S., Morrow, B., Karayiorgou, M., Antonarakis, S.E., Housman, D., et al. (1994). Psychotic illness in patients diagnosed with velo-cardio-facial syndrome and their relatives. J. Nerv. Ment. Dis. 182, 476–478.

Sekar A, Bialas AR, de Rivera H, Davis A, Hammond TR (2016). Schizophrenia risk from complex variation of complement component 4. Nature. 2016;530:177–183.

Swillen, A., Vogels, A., Devriendt, K., & Fryns, J. P. (2000). Chromosome 22q11 deletion syndrome: Update and review of the clinical features, cognitive-behavioral spectrum, and psychiatric complications. American Journal of Medical Genetics,97(2), 128-135. doi:10.1002/1096-8628(200022)97:2<128::aid-ajmg4>3.0.co;2-z