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Neuregulin 1, Brain Region Specificity and PI3K/Akt in Schizophrenia

Comment on "neuregulin 1 ICE-single nucleotide polymorphism in first episode schizophrenia correlates with cerebral activation in fronto-temporal area"

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Dear Editor: We read with great interest the paper "neuregulin 1 ICE-single nucleotide polymorphism in first episode schizophrenia correlates with cerebral activation in fronto-temporal area" published in your journal by Kircher et al. [3]. Based on blood cell NRG1 SNP data, it showed for the first time in the patients with schizophrenia that NRG1 SNP is associated with decreased cerebral activation in specific brain areas previously showing related to schizophrenia [3, 12]. Clearly, NRG1 gene mutation plays an important role in schizophrenia. It will be interesting to further explore why NRG1 SNP causes the activity changes in some brain areas but not others. We may not be able to directly link between the SNP and specific brain regional function and behaviour. The direct link is unlikely to be the case if SNP change is universal. NRG1 SNP caused signal pathway alteration may interact with brain region micro-environmental factors to cause the activity change. Therefore it is required to study the brain tissue in these regions under the condition of NRG1 SNP.

Heterogeneous changes in brain areas are very interesting. As we know brain is a very heterogenous structure, varying in neuronal and glial cell types, neurotransmitters and receptors and connections within and outside nuclei. We do know that neuregulin 1 acts on receptor protein kinase ErbB to conduct signal pathway for normal neural function [9]. The defects of the signals have associated with the pathogenesis of schizophrenia. Except neuregulin 1, ErbB mutation has also been detected in schizophrenia [5]. Decreased neuregulin 1/ErbB signals caused schizophrenia, through reducing the activity of PI3 K/Akt pathway. Thus, it is possible that other components of the signal pathway or other mutations that decrease PI3K/Akt may also cause changes. For example, inhibition of NMDAR can also reduce PI3K/Akt activity, leading to schizophrenia [1, 11]. The question will be what local structures may do to the intracellular signal transduction under the condition of NRG1 SNP and how it in turn changes cerebral function. While NRG1 SNP is universal, only some regions of brain showed activity change but others do not. This arises an interesting question that how changed PI3K/Akt signal pathway interacts with local environment to cause activity changes in those schizophrenia relevant areas.

The PI3K/Akt affects multiple aspects to cause schizophrenia. Via the reduction of PI3K/Akt activity, neuregulin 1 damages oligodendrote cells [10], Schwann cells [6], cell–cell interaction [2], axon guidance [7] and synapse number [4]. How these play roles in altered function of cerebral activation in fronto-temporal area as studied by authors is unknown. This could be further studied.

In general, we think that the study has further linked neuregulin 1 with the pathogenesis of schizophrenia and more investigation could be done in the interaction between neuregulin 1 SNP and brain regional features and the neuregulin 1/ErbB/PI3K/Akt pathway to associate them with schizophrenia. The correction of the pathway abnormality may be an approach for the prevention and treatment of schizophrenia. However, it must be noted that overexpression of neuregulins is carcinogenic [8].

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