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Commentary

Attention: Schizophrenia Risk Gene Product miR-137 Now Targeting *EFNB2*

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Schizophrenia is a complex disease believed to result from a combination of risk genes and environmental insults that change the trajectory of brain development. For decades researchers have strived to unravel the genetic complexity of schizophrenia, using a variety of approaches. If one can understand the nature of the risk genes, then we might better understand what causes schizophrenia, leading to better diagnosis and treatment strategies.

One underlying theme has been to relate changes in genes to biological dysfunction in the brain. Indeed, in the late 1990s many researchers turned to microarray analyses of gene expression in attempts to understand what genes have altered expression in the brain in schizophrenia (Mirnics et al., 2000) and hence what biological pathways might be affected. These studies showed that the expression of large numbers of genes is altered in the brains of people with schizophrenia (Bowden et al., 2008), but what caused this was unknown.

The central dogma of gene regulation that DNA codes for mRNA which is translated into proteins, was challenged by the discovery of a new mechanism for regulation of protein coding genes via non-coding RNA species including microRNAs (miRNA) (Lee et al., 1993). One single miRNA could bind to and affect hundreds of mRNA transcripts and might explain why so many genes are dysregulated in the brain in schizophrenia. Subsequent studies in the post-mortem brains from people with schizophrenia identified significant changes in miRNA expression (Beveridge et al., 2008). The potential importance of miRNA to understanding the molecular basis of schizophrenia was further highlighted when the Schizophrenia Working Group of the Psychiatric Genetics Consortium conducted the largest ever genome wide association study involving 36,989 cases and 113,075 controls (Ripke et al., 2014). One of the strongest findings was a link between schizophrenia and the genetic variant rs1625579 located in the intron that encodes a miRNA called miR-137 (Ripke et al., 2014). Since miRNA have hundreds of potential targets, the question is which miR-137 targets are relevant to schizophrenia and does this variant have any effect on its function?

Computational methods can identify the potential targets for a particular miRNA based on the seed sequence it uses to bind to usually the 3′-UTR of the target mRNA (Oulas et al., 2015). To determine which targets are relevant to schizophrenia and worthy of further investigation, Wu et al. (2016) searched their previous study of the *Han* Chinese (Zhang et al., 2010) to identify genes linked to schizophrenia that contain the target sequence for miR-137. *EFNB2* is such a gene that was linked to schizophrenia (Zhang et al., 2010), is functionally relevant to the disorder and is predicted to be targeted by miR-137. Wu and colleagues used luciferase reporter assays to show biologically that miR-137 targets the 3′ UTR of *EFNB2* and that the minor rs550067317 C allele variant at this site disrupted this interaction (Wu et al., 2016). With the interaction established, the task was then to determine whether miR-137 exerted its effects directly on the post-transcriptional levels of *EFNB2* mRNA or protein. In a neuroblastoma cell line commonly used for neurobiological studies, Wu and colleagues showed that miR-137 reduced the levels of endogenous *EFNB2* protein but not mRNA. This starts to tease out the mechanism used by miR-137 to influence the functional roles of *EFNB2*.

There is also great interest to use information from schizophrenia-associated genes as markers of schizophrenia phenotypes or as biomarkers to assist in diagnosis. To do this, brain biopsies are not feasible and ethical, so blood studies have been the main focus showing that some gene expression changes in blood mimic what is seen in the brain in schizophrenia (Sullivan et al., 2006). In 2013 a study showed that a variant in the *MIR137* gene when combined with severe negative symptoms identified a subtype of schizophrenia sufferers with cognitive deficits (Green et al., 2013). To further this line of research, Wu and colleagues showed that miR-137 but not *EFNB2* expression was increased in patients with schizophrenia compared to controls and that this had some diagnostic value in distinguishing patients from controls (Wu et al., 2016). Fig. 6B in the paper by Wu and colleagues shows that a subset of patients with schizophrenia have much higher miR-137 expression leaving you wondering what was their cognitive status?

Whilst the building evidence suggests miRNAs including miR-137 have a role in the development of schizophrenia and may have some capacity as biomarkers, clearly further collaborative efforts will determine how useful they are in understanding what causes schizophrenia, whether they can assist with its diagnosis and importantly, whether they provide insights on how to improve the current treatment options for the disorder.

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Disclosure

The author declared no conflicts of interest.

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