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Researchers reveal how brain-specific microRNA plays key role in causing abnormal brain development

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Autism Spectrum Disorders (ASDs) are a group of highly inheritable behavioural disorders that pose major personal and public health concerns. Patients with ASDs have mild to severe communication difficulties, repetitive behaviour and social challenges. Such disorders significantly challenge an individual's ability to conduct daily activities and function normally in society. Currently there are very few medication options that effectively treat ASDs.

Recognising a need to better understand the biology that produces ASD symptoms, scientists at Duke-NUS Medical School (Duke-NUS) and the National Neuroscience Institute (NNI), Singapore, have teamed up and identified a novel mechanism that potentially links abnormal brain development to the cause of ASDs. This new knowledge will help to improve the diagnosis and development of therapeutic interventions for ASDs.

In the study, published today in the journal *eLife*, co-senior authors Assistant Professor Shawn Je from Duke-NUS and Assistant Professor Zeng Li from NNI have shown how one brain-specific microRNA (miR-128) plays a key role in causing abnormal brain development. MicroRNAs are small molecules that regulate gene expression in the human body to ensure proper cellular functions. Although it was known that miR-128 is misregulated in some patients with autism, what that meant and how it functioned was not known.

The Duke-NUS and NNI team showed that miR-128 targets a protein called PCM1 that is critical to the cell division of neural precursor cells (NPCs). NPCs during early brain development have two fates - they either stay as NPCs and undergo self-renewal or become neurons through differentiation. The dysfunctional regulation of PCM1 by misregulated miR-128 impairs brain development, which may underlie brain size changes in people with ASDs.

"For the first time, we have managed to show that miR-128 is a mechanism that regulates early neuronal behaviour during brain development," said Asst Prof Je, from the Neuroscience and Behavioural Disorders (NBD) Programme at Duke-NUS. "Targeting this mechanism may be the answer to diagnose and treat ASDs that are caused by abnormal brain development."

Asst Prof Li, from the Neural Stem Cells Laboratory at NNI, added, "This important study suggests a link between a key neurological disease gene and regulation of microRNAs in the brain. However, we are just starting to understand how misregulated miR-128 expression can cause our brain activities to go wrong, and much more work needs to be done."

In a separate study which is not yet published, this team with Professor Steve Rozen, from the NBD Programme at Duke-NUS, identified many new mutations in the PCM1 gene from ASD patients from next-generation sequencing. Future work to correlate these mutations with functional consequences in brain development should not only increase the understanding of how autism is caused, but also enable a more accurate diagnosis of autism and other ASDs.

Source:
Duke-NUS Medical School
