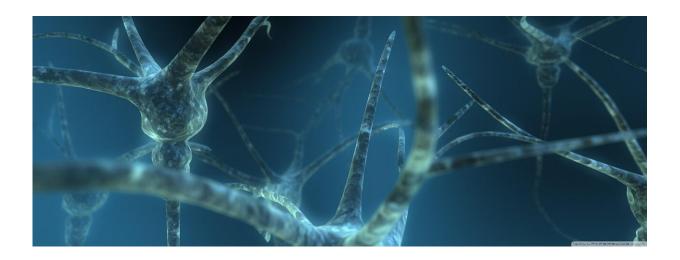


Study reveals link between brain cell development and risk of schizophrenia

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Scientists from Cardiff University have discovered new links between the breakdown in brain cell development and the risk of schizophrenia and other psychiatric disorders.

Genetic risk factors are known to disrupt brain development in a number of these disorders, but little is known about which aspects of this process are affected.

This research is the first time that genetic disruption of specific cell processes crucial to brain development has been linked to disease risk in



a wide range of psychiatric disorders.

The findings are published today in the journal *Nature Communications*.

The study was jointly led by Dr. Andrew Pocklington from the Division of Psychological Medicine and Clinical Neurosciences at Cardiff University and Dr. Eunju Jenny Shin from the Neuroscience and Mental Health Research Institute at Cardiff University and now at Keele University.

Dr. Pocklington said: "Genetic factors play a significant role in determining a person's risk of developing psychiatric disorders. Uncovering biological processes impacted by these genetic risk factors is a major step towards understanding the causes of disease."

Dr. Shin said: "To truly understand the root causes of psychiatric disorders, we focused on studying the development of brain <u>cells</u>. The knowledge gained through this approach may ultimately help guide the development of novel therapies or help explain why some individuals respond to some treatments but not others."

The scientists studied the birth and early development of human brain cells—a process known as neurogenesis—in vitro using human pluripotent stem cells.

They identified several sets of genes that are switched on during neurogenesis—both in vitro and in human foetal brain—with each set appearing to play a distinct functional role. The researchers showed that genetic risk factors contributing to schizophrenia and other psychiatric disorders were highly concentrated in these sets.

Dr. Shin said: "In vitro experiments showed that when activation of these sets is disrupted, the shape, movement and electrical activity of



developing brain cells is altered, linking changes in these properties to disease."

Disorders linked to disruption of these genes included both early onset conditions (<u>developmental delay</u>, autism and ADHD) and, more surprisingly, conditions with a later onset (bipolar disorder, major depression) for which disruption of early <u>brain development</u> is not generally thought to play a large role.

This raises the question of whether some of these genes—which are first switched on long before birth—remain active later in life and contribute to mature brain function, where they can potentially be targeted therapeutically.

Dr. Pocklington said: "Previous studies have shown that genes active in mature brain cells are enriched for common genetic variants contributing to schizophrenia. Much of this enrichment was captured by the early developmental gene sets, which seem to contain a greater burden of common genetic risk factors.

"This suggests that some biological pathways first switched on in the early pre-natal brain may remain active in later life, with genetic variation in these pathways contributing to disease by disrupting both development and mature brain function."

Further work is needed to map out the full range of developmental processes disrupted in different psychiatric disorders and explore their longer-term effects on the <u>brain</u>.

Dr. Shin said: "Although much remains to be uncovered, our findings provide valuable insight into the developmental origins of <u>psychiatric</u> <u>disorders</u> such as schizophrenia."



More information: Transcriptional programs regulating neuronal differentiation are disrupted in DLG2 knockout human embryonic stem cells and enriched for schizophrenia and related disorders risk variants, *Nature Communications* (2022). DOI: 10.1038/s41467-021-27601-0

Provided by Cardiff University

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