Important step towards accurate use of stem cell–based disease models

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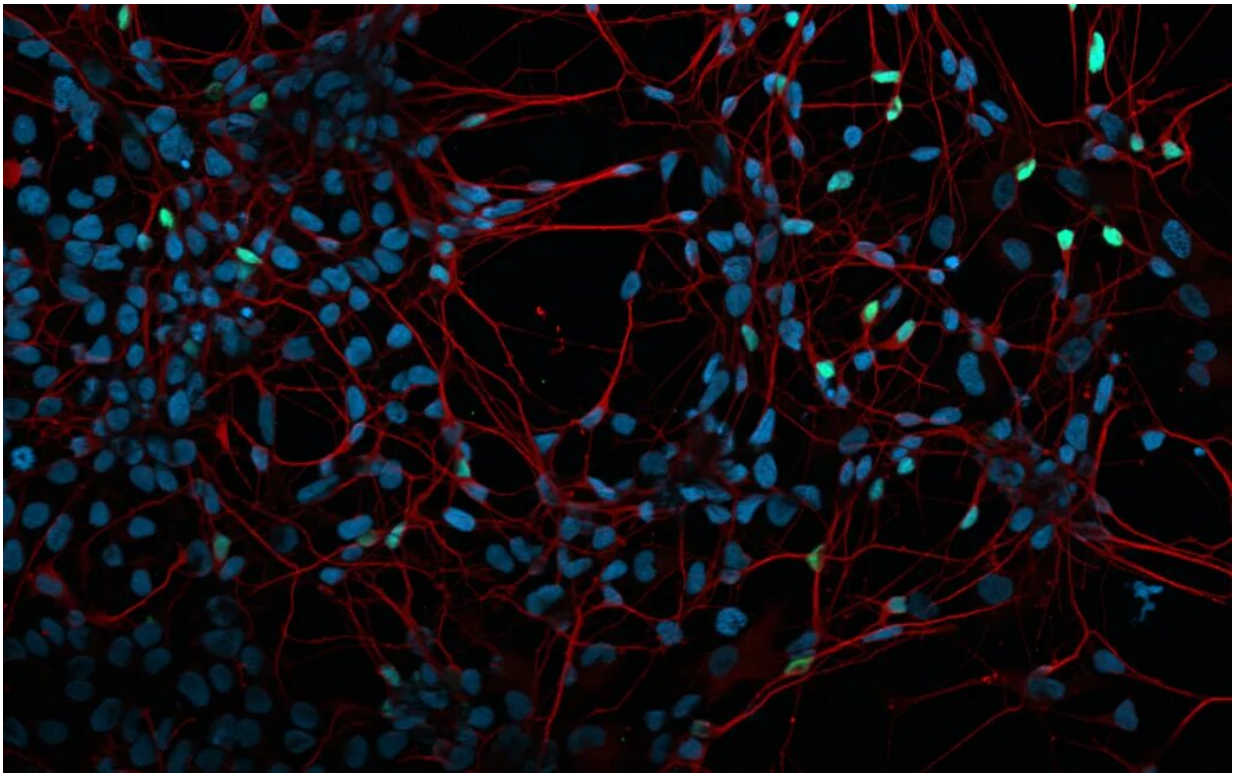

Fluorescent microscopy image of cultured neurons derived from iPSC lines. Credit: Group Kilpinen

Induced pluripotent stem cells offer great therapeutic potential and are a valuable tool for understanding how different diseases develop. New research shows that such stem cell lines should be regularly screened for

genetic mutations to ensure the accuracy of the disease models.

In the past 10 years, scientists have learned to create induced pluripotent stem cells (iPSC) from ordinary cells by genetic reprogramming. These cells are widely used to study diseases, as they can be differentiated to almost any cell type of the body, and they can be generated from any individual. However, a key remaining methodological challenge is that the differentiation process is subject to major technical variation for mostly unknown reasons.

HiLIFE Tenure Track Professor Helena Kilpinen and her group at the University of Helsinki use stem cells for studying the biological mechanisms of neurodevelopmental and other brain-related diseases.

Their new study, just published in the journal *Cell Genomics*, aimed to shed light on the reasons for the variable differentiation outcomes of iPSCs. This collaborative research from the University of Helsinki and University College London demonstrates that cultured stem cells may acquire new genetic mutations that can have a significant impact on the differentiation capability of the cells.

The researchers examined the role of such mutations by following the differentiation of more than 200 iPSC lines from healthy individuals to dopaminergic neurons and by comparing the differentiation outcome with the mutation profile. They used a technology that analyzes one cell at a time to follow the differentiation trajectories of individual neurons.

The researchers observed that those iPSC lines with damaging mutations in a gene called BCOR produced less neurons, proliferated faster in culture and presented large differences in gene expression. This gene is a key regulator during normal embryonic development.

"In line with our original hypothesis, the results showed that mutations

acquired during the generation and subsequent culture of iPSC lines can have a major effect on the differentiation process, completely independently from any disease-specific processes," Dr. Kilpinen says.

The team also discovered that the mutational processes that compromise the production of neurons in the laboratory conditions share some similarities with those present during brain formation.

"Surprisingly, somatic mutations found in iPSCs lines impacted the same genes mutated during early human brain development. If those mutations can be mirrored, we will have a very detailed picture of the genetic factors that cause neurodevelopmental disease," the first author of the study, Pau Puigdevall who works as a postdoctoral researcher in Helena Kilpinen's group, says.

The researchers concluded that their findings call for caution when interpreting differentiation-related phenotypes using iPSC models to understand disease.

"Based on this data, more optimization in the laboratory is needed to generate good disease models and eventually use them at scale with patients, specifically in developmental and neuropsychiatric disorders," Dr. Kilpinen says.

More information: Pau Puigdevall et al, Somatic mutations alter the differentiation outcomes of iPSC-derived neurons, *Cell Genomics* (2023). DOI: 10.1016/j.xgen.2023.100280

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