A key role for CEP63 in brain development and fertility discovered

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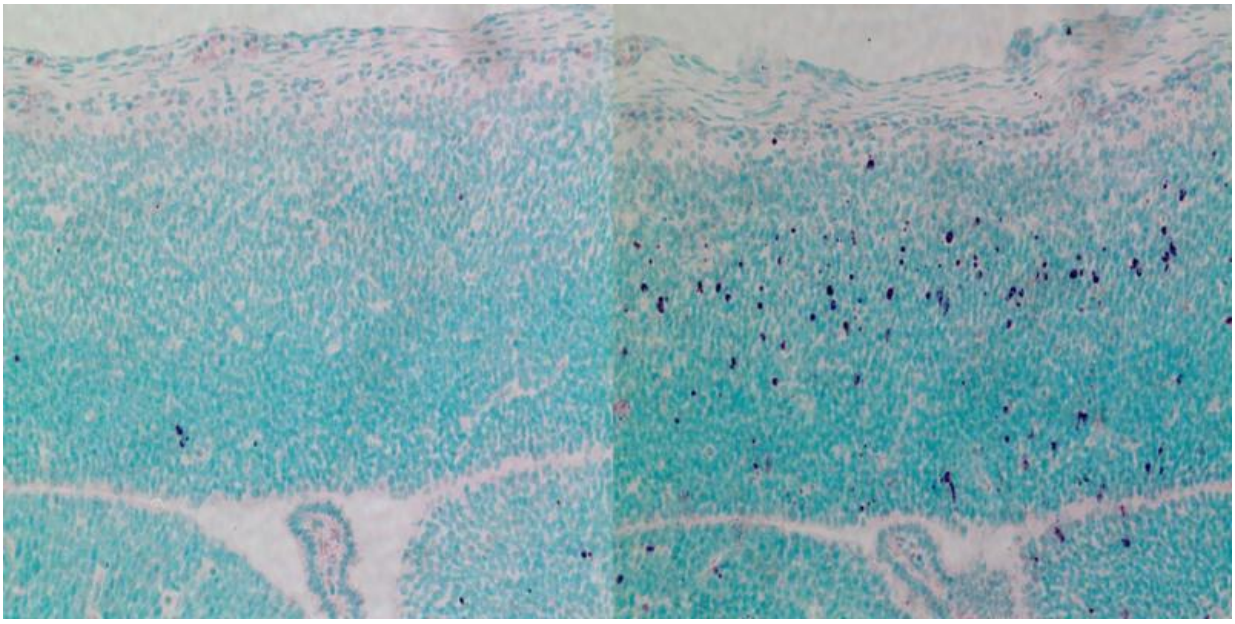

CEP63 depletion increases stem cell death in the developing mouse brain. The image on the right shows the stem dying cells in purple. The mice are born with microcephaly, a characteristic feature of Seckel syndrome. Credit: Berta Terré, IRB Barcelona

Today in *Nature Communications*, scientists at the Institute for Research in Biomedicine (IRB Barcelona) provide molecular details about Seckel Syndrome, a rare disease that causes microcephaly, or small brain, and growth delays. A joint study conducted by Travis Stracker and Jens

Lüders indicates that the protein CEP63 plays a key role during brain development as it is involved in the correct division of stem cells in this organ. Furthermore, the researchers have discovered that CEP63 is associated with sperm production—an unknown function until now.

Rescuing microcephaly in mice

There are no treatment options for microcephaly to date. This defect in brain growth is present in several neurodevelopmental diseases, including Seckel Syndrome. "There are diagnostic tests for some of these kinds of pathologies that can be performed during pregnancy, but other than early detection, the expectant parents are limited to two choices, either to abort or to continue with the pregnancy, being fully aware of the outcome," explains the North American scientist Travis Stracker. "Our research paves the way to explore therapeutic approaches for microcephaly involving the inhibition of the protein p53," says the head of the Genomic Instability and Cancer Lab at IRB Barcelona.

The scientists describe that this protein triggers the death of brain stem cells. This occurs because cells without CEP63 have delayed cell division, leading them to enter programmed cell death through p53. "Cell death due to mutations in CEP63 is the main cause of the brain defects. When we prevent cell death by removing p53 from developing embryos, the brain develops to its normal size," explains Jens Lüders, head of the Microtubule Organization Lab.

This finding paves the way to study whether p53 inhibitors could provide the basis of a future treatment to prevent microcephaly. "It is early to say that we have a treatment proposal for humans because we are in the first stage of discovery. Also, a normal sized brain does not imply a functional brain," warn the researchers. "Our next goal is to test the p53 inhibitors currently available in the same mouse models and to characterise and analyse the long-term effects. Furthermore, p53

inhibition could be harmful because this gene has many functions in correct embryonic development," they add.

Infertility

The study also revealed that CEP63 is related to fertility in male mice. The researchers have discovered that this protein is involved in sperm production and, when absent, mice show severe infertility. "We know that CEP63 depletion leads to problems during meiosis, a specialized type of cell division that is required for male germ cells to produce sperm," explains Stracker. "It is an interesting finding because in many cases fertility problems are not widely understood and this study provides a different molecular perspective to examine," says Lüders.

More information: CEP63 deficiency promotes p53 dependent microcephaly and reveals a role for the centrosome in meiotic recombination, Marko Marjanović, Carlos Sánchez-Huertas, Berta Terré, Rocío Gómez, Jan Frederik Scheel, Sarai Pacheco, Philip A. Knobel, Ana Martínez-Marchal, Suvi Aivio, Lluis Palenzuela, Uwe Wolfrum, Peter J. McKinnon, José A. Suja, Ignasi Roig, Vincenzo Costanzo, Jens Lüders, and Travis H. Stracker, *Nature Communications* (July 2015): DOI: 10.1038/ncomms8676

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