# Nijmegen breakage syndrome: Molecular pathways that lead to microcephaly

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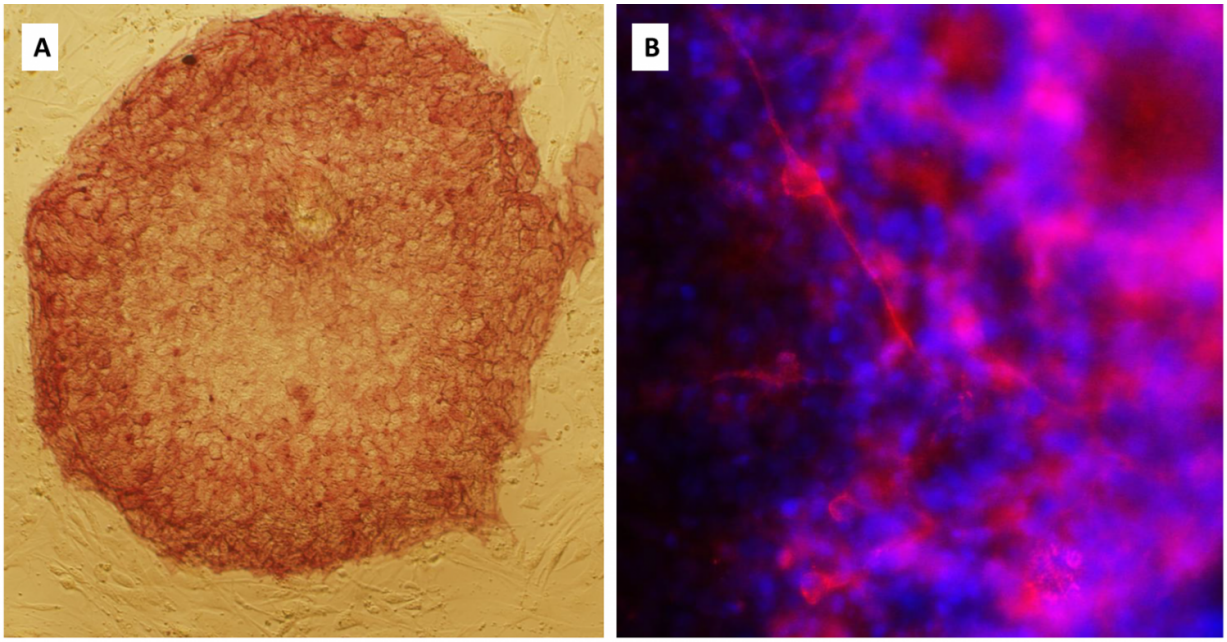


A. Skin cells from NBS patients were reprogrammed into induced pluripotent stem cells that form a round, flat colony and stained positive for alkaline phosphatase activity, an early marker for pluripotency. B. The induced pluripotent stem cells with NBS were then differentiated into early neurons, showing the formation of neural rosettes and neurons. These cells were stained positive for NCAM1 (red), a protein expressed in early neurons (nuclei stained in blue). Credit: Tomer Halevy et. al.

Scientists from Jerusalem and Duesseldorf have succeeded in generating

induced pluripotent stem cells from a rare disorder called Nijmegen breakage syndrome (NBS) and to push these cells to become early neurons, revealing the mechanisms leading to the neurological phenotype observed in these patients.

Nijmegen breakage syndrome is a devastating disorder in which the affected children suffer from pronounced microcephaly, cognitive impairments, dwarfism, strong cancer predisposition, and immunodeficiency. The syndrome is caused when a child receives a mutant NBS1 gene from both his parents. It was known that the NBS1 gene is important for the recognition of breaks in the DNA of the child, explaining the cancer predisposition and immunodeficiency of the patients. However, it was not clear how this gene affects the development of the brain and why the affected children suffer from smaller brains. Therefore, the generation of induced pluripotent stem cells from patients and the ability to turn them into neurons, as published in the latest issue of the journal *Cell Reports*, gave scientists the opportunity to study the causes for brain impairment as seen in affected children.

Prof. Michal Goldberg and Prof. Nissim Benvenisty from the Hebrew University of Jerusalem, together with Prof. James Adjaye from the Heinrich Heine University in Duesseldorf, in a study led by graduate student Tomer Halevy, succeeded in generating induced pluripotent stem cells from two patients, a boy and a girl, carrying the syndrome, and looked at different characteristic of the cells. Previous studies to understand the disorder were performed on skin cells, and so the causes for the neural pathologies were unknown.

Surprisingly, in this study, the investigators found that P53, a gene with a well known role in preventing cancer may also be responsible for the neural phenotype of Nijmegen breakage syndrome. P53 was demonstrated to be a target of the NBS1 gene, and an emerging role for

P53 in early neural development has been suggested. In this study, the researchers have found that since NBS1 is missing in patients' neurons P53 cannot work properly, this in turn leads to cancer development but also affects the early development of the nervous system.

According to Prof. Goldberg, a researcher from the Department of Genetic at the Hebrew University of Jerusalem and principal co-author of the study "Induced pluripotent stem cells derived from Nijmegen breakage syndrome patients provide a powerful tool to study different aspects of the disease, mainly the neural phenotype, as we are able to turn these cells into neural cells and study the developmental aspects of the disorder that could not have been studied before. We can now zoom in and detect dysregulated molecular pathways in neuron derived from patient cells and understand how they affect the children with the disorder. Furthermore, since many diseases resulting from mutations in genes that are important for genomic stability show apart from cancer predisposition also neurological phenotypes, our findings may serve as a platform for the study of additional genomic stability syndromes and pave the way for elucidating the crosstalk between genomic stability and neurological impairments".

Two great advantages of induced pluripotent cells that carry the disorder have on previously used cells, are their ability to become any cell type that we want to study, and their limitless replication potential. We can thus use these cells to perform drug screenings to test for compounds to correct some of the dysregulated pathways that we discovered to be involved in the development of the syndrome. This will be done in our case on derived neural cells but can be performed on any other cell type depending on the tissue we wish to treat.

The cells that were generated and the mechanism underlying the neural phenotype of Nijmegen breakage syndrome, which was discovered in this work will greatly facilitate in the search for a treatment for affected

children and also in our understanding of related disorders associated with problems in DNA breaks recognition that have a similar neural phenotype.

According to Prof. Adjaye, Director of the Institute for stem cell research and regenerative medicine, the established and additional NBS induced pluripotent stem cell lines will serve as useful in vitro models to study the underlying mechanism(s) linking impaired neurogenesis to microcephaly by establishing NBS-derived brain organoids and comparing these to organoids derived from healthy individuals.

**More information:** Tomer Halevy,Shira Akov, Martina Bohndorf, Barbara Mlody, James Adjaye, Nissim Benvenisty and. Michal Goldberg (2016). Chromosomal Instability and Molecular Defects in Induced Pluripotent Stem Cells from Nijmegen Breakage Syndrome Patients. *Cell Reports* 16, 1-13

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