Glioblastoma and autism: Possible mechanism for neuronal malformation discovered

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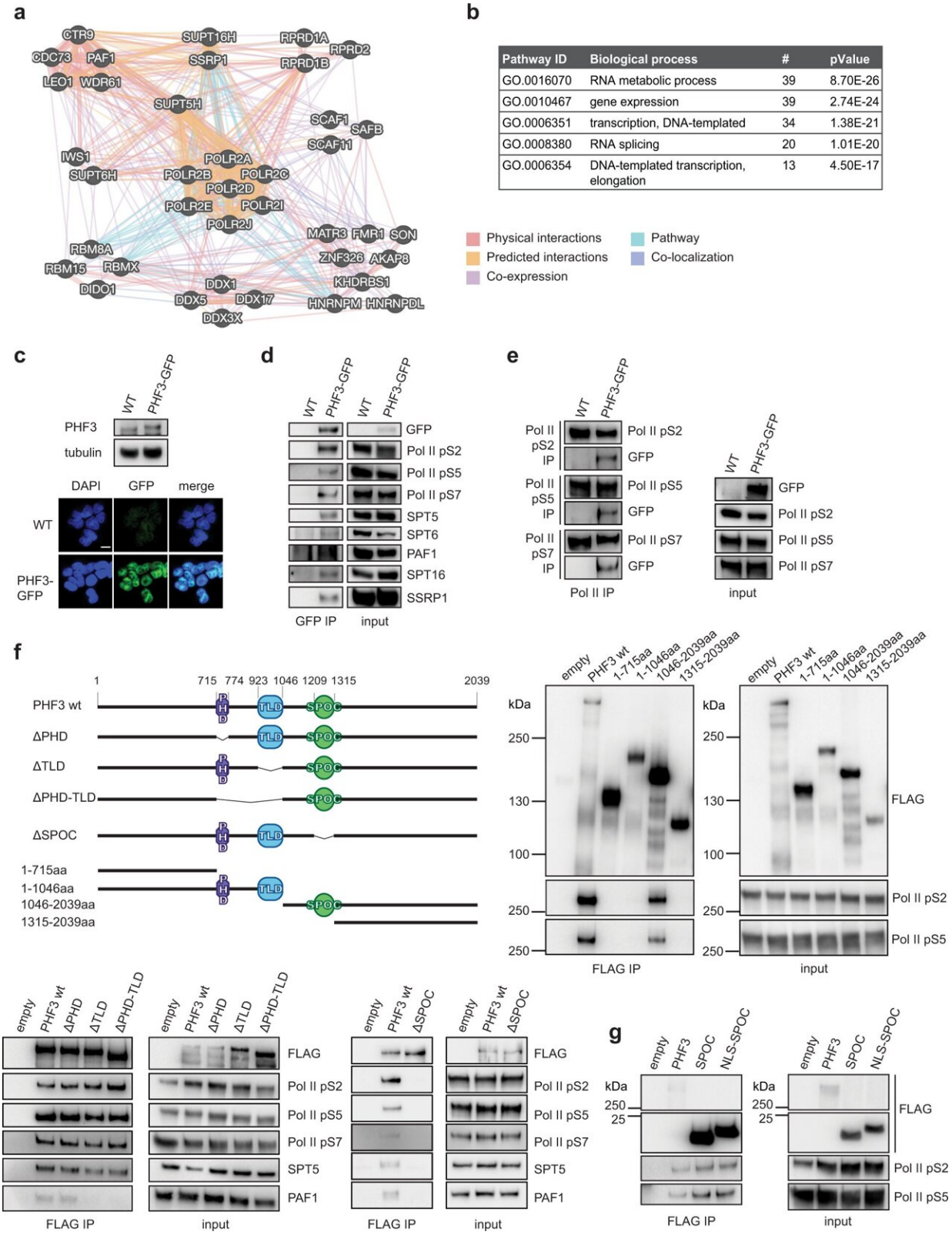

Fig. 1: PHF3 interacts with RNA polymerase II via the SPOC domain. a

GeneMANIA135 interaction map of the PHF3 interactome. b Gene ontology biological processes of the PHF3 interactome revealed by mass spectrometry. c Expression levels and nuclear localization of PHF3-GFP in the endogenously tagged HEK293T cell line revealed by Western blotting with anti-PHF3 and fluorescence microscopy. Scale bar = 10 μm. The experiment was performed once. d PHF3-GFP was immunoprecipitated using anti-GFP. Pol II phosphoisoforms, as well as transcription regulators SPT5, SPT6, PAF1, and FACT complex (SPT16 and SSRP1) were detected in the eluates. The experiment was performed once. e Endogenous Pol II phosphoisoforms were immunoprecipitated from PHF3-GFP cells and PHF3-GFP was detected in the eluates. The experiment was performed once. f Anti-FLAG immunoprecipitation of FLAG-PHF3 deletion mutants. Pol II does not co-immunoprecipitate in the absence of the PHF3 SPOC domain. The experiment was performed four times. Representative blots are shown. g Anti-FLAG immunoprecipitation of the FLAG-SPOC domain shows interaction with Pol II. The experiment was performed once. Credit: DOI: 10.1038/s41467-021-26360-2

In accordance with the blueprint contained in our DNA, human cells produce proteins that perform specific functions. An essential step in this process is the reading of the DNA and the transcription of the information into mRNA. A multi-center study with significant participation from MedUni Vienna has now shown for the first time that a specific protein, PHF3, plays an important role in transcription: its binding to the enzyme RNA polymerase II (POL II) modulates the reading process. PHF3 binds to POL II via a specific site on its surface called the SPOC domain. If SPOC is defective or absent, PHF3 cannot bind, and neuronal production defects occur. This could be one of the causes of autism and glioblastoma. The study has now been published in the renowned journal *Nature Communications*.

The paper focuses on the protein PHF3. It was known that autistic people often exhibit mutations in PHF3 and that only very low levels of

PHF3 are found in glioblastomas (the most common type of malignant brain tumor).

The study leader is Dea Slade, a molecular biologist at Max Perutz Labs (a joint venture between the Medical University of Vienna and the University of Vienna) and, since September 2021, at the Department of Radiation Oncology of MedUni Vienna and Vienna General Hospital, as well as a member of the Comprehensive Cancer Center of the two institutions. She explains: "In the paper, we were not only the first research team in the world to demonstrate that PHF3 is a transcription factor and that it binds to POL II via the SPOC domain but we were also able to show that the protein significantly influences neuronal differentiation, through the SPOC domain. If the protein was missing, neurons could not be formed, suggesting a correlation between the absence of PHF3 or SPOC and the development of autism and glioblastoma."

Comprehensive study

The study was performed on cell lines and was carried out from different angles. Slade explains: "We studied the biochemical interaction of PHF3 or SPOC with POL II as well as its interaction at the cellular level, that is to say how the protein affects cellular function. Last but not least, we also looked at the level of differentiation, that is, how the cellular network is affected. This gives us a very detailed insight into the role that PHF3 plays in neuronal cell development."

In order to obtain results that are applicable humans, in a next step the team would like to test their findings in an animal model.

More information: Lisa-Marie Appel et al, PHF3 regulates neuronal gene expression through the Pol II CTD reader domain SPOC, *Nature Communications* (2021). DOI: 10.1038/s41467-021-26360-2