Researchers uncover how a microtubule-related gene affects neural development

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The mechanism linking cortical developmental disorders with a gene related to key structural components of cells known as microtubules has been uncovered by A*STAR scientists. The discovery improves our understanding of the pathology of the disorders and expands the range of genes known to be involved in neurodevelopment.

Microcephaly and lissencephaly are disorders in which brains develop to be abnormally small or abnormally smooth, respectively. In 2014, Bruno Reversade's team at the A*STAR Institute of Medical Biology and Chris Walsh's lab at Harvard showed that patients with both disorders—microlissencephaly—carry a mutated version of the P80 gene, which encodes a subunit of the KATNB1 gene. In a follow-up paper, the Reversade lab and their collaborators in Japan have uncovered the mechanism linking P80 to these symptoms.

The study began with a search for proteins that interact with P80. To the researchers' surprise, they discovered an interaction with NuMA, a well-studied protein which organizes microtubules during mitosis. They also confirmed that P80 binds to dynein, a molecular motor associated with microtubules that had already been identified as a P80 partner.

The researchers then investigated how these proteins regulate microtubules during mitosis. They showed that P80 and NuMA use dynein as a motor to shuffle between the nucleus and the centrosome, a microtubule organizing center that plays a crucial role in mitosis. The lack of either protein led to abnormal mitosis. Mutations in P80 linked

with microlissencephaly impaired its interaction with dynein or with microtubules, suggesting that the P80-NuMA-dynein network plays a role in these disorders.

"The most elegant assay we did was the in vitro aster formation," says Oz Pomp, a scientist in the Reversade lab who co-led this project. Asters are microtubule arrays formed during mitosis around the centrosome, an organelle which forms microtubules and regulates the cell cycle, and Pomp was amazed to find that combining P80, NuMA, dynein, microtubules, and the energy-storage molecule ATP in a test tube was enough for asters to form.

Finally, the team showed that P80 and NuMA activity in the centrosome is essential for neural development. In mouse embryos, neurons lacking either protein differentiated early, divided insufficiently, and migrated abnormally.

"With each gene causing a similar phenotype, we are adding more pieces to the puzzle. By connecting the dots we will eventually get the big picture of how a human brain is built," says Reversade. In the meantime, each gene they identify improves the prospects of genetic counseling and screening and provides a new avenue for researchers studying brain disorders.

More information: Mingyue Jin et al. Katanin p80, NuMA and cytoplasmic dynein cooperate to control microtubule dynamics, *Scientific Reports* (2017). DOI: 10.1038/srep39902

Wen F. Hu et al. Katanin p80 Regulates Human Cortical Development by Limiting Centriole and Cilia Number, *Neuron* (2014). DOI: 10.1016/j.neuron.2014.12.017

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