

INTERVIEW

The people behind the papers – Alexander Phillips and David Keays

Certain mutations in end-binding (EB) protein 2, a member of the EB family of conserved microtubule plus-end tracking proteins, are implicated in a rare syndromic form of microcephaly. While the two other EB family members – EB1 and EB3 – have been the subject of intense study, the cellular role of EB2 is not clearly understood. In their work, [Alexander \(Alex\) Phillips, David Keays and colleagues](#) show that EB2 is necessary for maintaining mitotic fidelity during embryonic brain development in mouse and human. To learn more about their work, we spoke to the first author, Alex Phillips, and the corresponding author, David Keays, Adjunct Investigator at the Research Institute of Molecular Pathology (IMP), Austria, and Professor at the Ludwig-Maximilians-Universität München, Germany.

David, what questions are you trying to answer in your lab?

DK: We are interested in how biology constructs a vertebrate brain. It's arguably the most complex structure in the universe, with billions of neurons and trillions of synapses, but its blueprint relies on a simple four-letter genetic code. We have focused on the microtubule cytoskeleton, which forms the key building blocks in every neuron.

Alex, how did you come to work in the lab and what drives your research today?

AP: I did my Master's thesis in Madeline Lancaster's lab at the Medical Research Council (MRC) Laboratory of Molecular Biology (LMB), Cambridge, where I became fascinated by the molecular logic determining how neural progenitor cells divide. I knew that I wanted to study neural progenitor cell division by focusing on human disease during my PhD, and the Keays lab has a reputation as a place where you can do rigorous science, while also having a lot of fun! As soon as Dave told me about the individuals with microcephaly harbouring EB2 mutations, I was hooked.

Can you tell us about the background of the field that inspired your work?

DK & AP: Hilde Van Esch's lab previously showed that mutations in EB2 and the β -tubulin TUBB5 (TUBB) cause an unusual disease state in human, characterised by excessive skin folding, intellectual impairment and microcephaly (Isrie et al., 2015). Our laboratory had implicated TUBB5 in a spectrum of neurodevelopmental disease states, and we were eager to explore how EB2 might contribute. While its more famous brethren, EB1 and EB3, had been investigated at length, little was known about the molecular and cellular function of EB2.



David Keays (left) and Alex Phillips (right) in the lab. Credit: L. Beck/IMP, Vienna.

What are the key results of the paper?

DK & AP: In this paper, we show that EB2 is recruited to the mitotic spindle in neuronal progenitors. Exploiting unique mouse and human stem cells (generously shared by the Van Esch lab), we demonstrate that a loss-of-function disease-causing mutation (Q152X) stalls mitosis in prometaphase, causes defects in chromosome congression and finally leads to p53-induced apoptosis. The end result is a microcephalic brain.

When doing the research, did you have any particular result or eureka moment that has stuck with you?

AP: Not much was known about EB2 when we began the project, and we had lots of different hypotheses about how mutations in this protein may affect brain development. The eureka moment came when I did an immunofluorescence stain using a mitotic cell marker. In the mutant mice, the brains literally lit up, suggesting that there were more cells in mitosis. Once we knew we were dealing with a mitotic phenotype, we were able to build on the work of researchers like Debra Silver, Renata Basto and Andrew Holland to generate and test hypotheses about the cellular mechanisms underlying this phenotype.

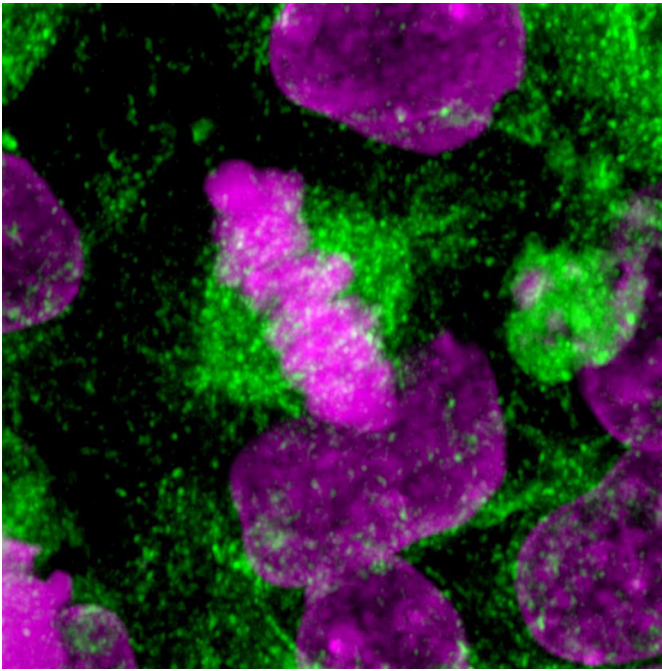
And what about the flipside: any moments of frustration or despair?

AP: In the midst of my PhD, the covid pandemic struck. Instead of spending time in the lab, Dave and I walked the empty streets of Vienna in our N95 masks imagining experiments that could be done. We had grand proteomic plans. Yet as the world lurched from one outbreak to the next, it felt like these ambitions were constantly being thwarted.

Why did you choose to submit this paper to Development?

DK & AP: Development was our first port of call for this manuscript. The journal has a reputation for publishing influential

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A human neural progenitor undergoing mitosis. The microtubule-associated protein EB2 is shown in green and DNA in magenta.

papers that stand the test of time, reflecting the critical but fair review process. Scientific publishing is increasingly predatory, expensive and driven by scientific fashion over cold hard facts. It is a credit to The Company of Biologists that they have resisted this trend.

Alex, what is next for you after this paper?

AP: I am currently a Senior Research Assistant in the Clemens Plaschka lab at the Research Institute of Molecular Pathology

(IMP), Vienna. This year, I will be starting a science podcast, and my daughter will be born in July – so, I have a lot to keep me busy!

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David, where will this story take your lab next?

DK: This paper has highlighted the utility of combining mouse and human stem cell models to gain mechanistic insight into a disease state. In the future, we will build on this approach, investing in 2D and 3D cell culture models to study neurodevelopmental disorders. In doing so, we hope to shed further light on the genetic architecture required to build a human brain.

Finally, let's move outside the lab – what do you like to do in your spare time?

DK: I grew up in Australia, a continent marked by extraordinary natural beauty and a large collection of weird plants and animals. I jump at any opportunity to hire a four-wheel drive (a Toyota Landcruiser 70 series) and drive off into the bush, with a good book (about birds), a map (that can be read on the bonnet of your car) and an Esky full of cold beer.

AP: In my spare time, I enjoy spending time with my family, exploring the Austrian countryside and taking bike rides with my son.

Reference

Isrie, M., Breuss, M., Tian, G., Hansen, A. H., Cristofoli, F., Morandell, J., Kupchinsky, Z. A., Sifrim, A., Rodriguez-Rodriguez, C. M., Dapena, et al. (2015). Mutations in either TUBB or MAPRE2 cause circumferential skin creases Kunze type. *Am. J. Hum. Genet.* **97**, 790-800. doi:10.1016/j.ajhg.2015.10.014
Phillips, A. W., Cushion, T. D., Vilceanu, A., Heisterkamp, P. and Keays, D. A. (2026). Loss of EB2 delays mitotic progression in murine and human neural progenitors. *Development* **153**, dev204903. doi:10.1242/dev.204903