© 2023. Published by The Company of Biologists Ltd | Disease Models & Mechanisms (2023) 16, dmm050192. doi:10.1242/dmm.050192

FIRST PERSON

First person – Brittany Truong

First Person is a series of interviews with the first authors of a selection of papers published in Disease Models & Mechanisms, helping researchers promote themselves alongside their papers. Brittany Truong is first author on 'PRDM1 DNA-binding zinc finger domain is required for normal limb development and is disrupted in split hand/foot malformation', published in DMM. Brittany is a PhD Student in the lab of Kristin B. Artinger at the University of Colorado Anschutz Medical Campus, Aurora, CO, USA, investigating the molecular and genetic mechanisms involved in the development of the limb.

Brittany Truong

How would you explain the main findings of your paper to non-scientific family and friends?

In this paper, we studied a congenital disease called split hand/foot malformation (SHFM) using zebrafish as a model. Zebrafish pectoral fins are homologous to mammalian forelimbs. The mechanisms involved in limb/fin development are highly conserved, so we can use zebrafish as a tool for studying this disease. Individuals with SHFM have missing, shortened, or fusions in their fingers and/or toes. SHFM is associated with a set of known genetic variants, but in 50% of cases, the cause is unknown. Here, we identified three families with SHFM who do not test positive for known variants, but they have novel, pathogenic variants in a gene encoding a transcription factor, *PRDM1*. We show that these variants impede limb development by disrupting the ability of the protein to regulate key limb genes. More specifically, PRDM1 must be able to bind to DNA at its zinc finger domain and activate genes that are involved in limb induction, outgrowth, differentiation and anterior/posterior patterning, i.e. the formation of our digits. Our work improves our overall understanding of the mechanisms governing limb and pectoral fin development and introduces novel *PRDM1* variants linked to SHFM.

"Individuals with SHFM have missing, shortened, or fusions in their fingers and/or toes. SHFM is associated with a set of known genetic variants, but in 50% of cases, the cause is unknown."

What are the potential implications of these results for your field of research?

We have identified novel *PRDM1* variants and show that they are linked to SHFM phenotypes. This will be useful to clinicians as well as SHFM individuals who don't know the genetic cause of their limb defects. Moreover, our work improves our overall understanding of the gene regulatory networks involved in limb and pectoral fin development.

What are the main advantages and drawbacks of the experimental system you have used as it relates to the disease you are investigating?

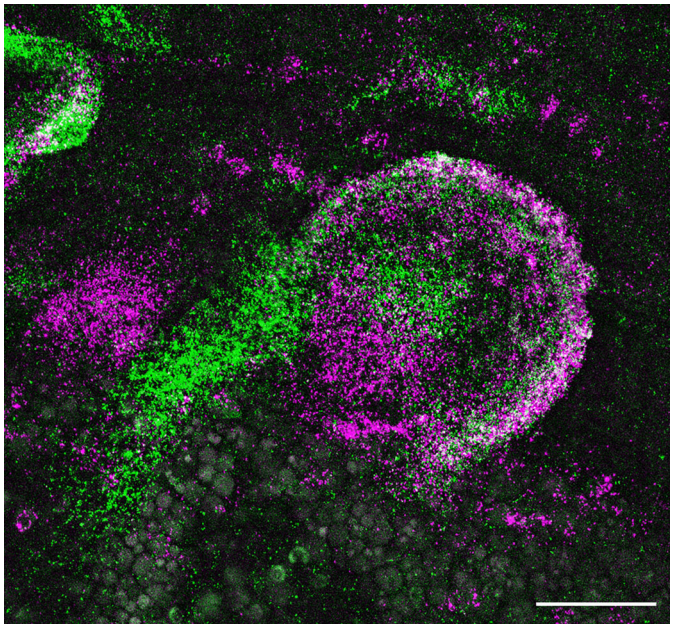
Zebrafish are a powerful genetic tool because they grow quickly, are relatively easy to genetically manipulate, and are transparent during early development, allowing us to better visualize gene expression. In addition, zebrafish pectoral fins are homologous to mammalian forelimbs, and the gene regulatory networks involved are highly conserved. With that said, fins and limbs are still quite distinct from one another, and our study can only provide hints into what is happening in human limb development.

What has surprised you the most while conducting your research?

I was most surprised by the changes in *dlx5a* expression in our *prdm1a*$^{-/-}$ zebrafish mutants. *dlx5a* is a marker of outgrowth, and, given the truncated fin phenotype observed in *prdm1a*$^{-/-}$ mutants, we expected to see a significant decrease in *dlx5a* expression throughout the fin. I performed hybridization chain reaction (HCR) at 48 h post fertilization and saw that *dlx5a* is decreased in the fin mesenchyme and cleithrum of *prdm1a*$^{-/-}$ mutants, as expected, but increased in the apical fold. The data suggest that the apical fold is highly disrupted with the loss of Prdm1a.

Brittany Truong's contact details: University of Colorado Anschutz Medical Campus, 12801 E. 17th Ave, MS 8120, Aurora, CO 80045, USA.
E-mail: brittany.truong@cuanschutz.edu

Disease Models & Mechanisms (2023) 16, dmm050192. doi:10.1242/dmm.050192



Lateral view of the zebrafish pectoral fin at 48 h post fertilization showing the expression of *prdm1a* (magenta) and *dlx5a* (green). Proximal, left. Scale bar: 50 µm.

What do you think is the most significant challenge impacting your research at this time and how will this be addressed over the next 10 years?

At this time, creating single point mutations in zebrafish is still very difficult. We initially planned on introducing each of the SHFM *PRDM1* variants into zebrafish using CRISPR/Cas9, but this was challenging. Over the next 10 years, this will likely become easier.

What changes do you think could improve the professional lives of scientists?

Research can be incredibly taxing, but we must remember that it should not dictate every part of our lives. Taking a step back and maintaining a healthy work/life balance can help reduce stress and prevent burnout.

What's next for you?

After defending my dissertation in April 2023, I am pursuing a career in science writing. My goal is to make science more accessible to the general public while staying up to date on the latest advancements in the field.

Reference

Truong, B. T., Shull, L. C., Lencer, E., Bend, E. G., Field, M., Blue, E. E., Bamshad, M. J., Skinner, C., Everman, D., Schwartz, C. E. et al. (2023). PRDM1 DNA-binding zinc finger domain is required for normal limb development and is disrupted in split hand/foot malformation. *Dis. Model. Mech.* **16**, dmm049977. doi:10.1242/dmm.049977