Researchers unravel mystery in search for connective tissue disease causes

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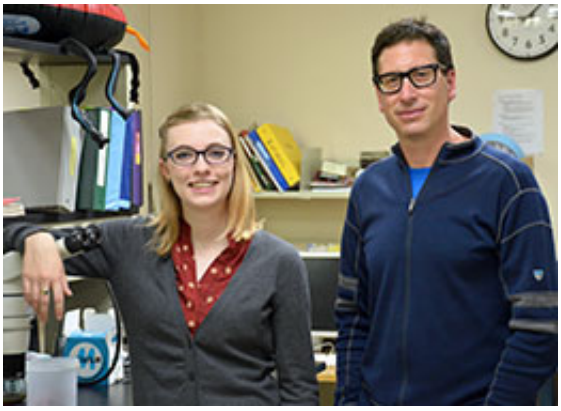

Research by Ph.D. student Melissa Kelley and Professor David Fay discovered, in C. elegans, intrinsic biomechanical forces operating in embryos no one had previously theorized. Credit: UW Photo

University of Wyoming molecular biologist David Fay doesn't much look like famous sleuths such as television's Columbo—no trenchcoat, at least—nor Fox Mulder of "X Files" fame; there is no doubting-what's-out-there Scully at his side.

Fay earned his Ph.D. in molecular biophysics and biochemistry from Yale University, and his laboratory logo is a worm with a boot (emphasis on singular boot) and spur, sporting a red neckerchief, and donning a hat with a "W"—"The Wyoming Worm Lab."

His scientific journal articles total 48 and date back to 1991.

And yet, there is no denying the look of fun that spreads across his face when this director of the Molecular and Cellular Life Sciences (MCLS) Program at UW talks about the mystery he and his lab associates pursued, tracked down and ultimately solved.

It began with mutant worms.

"This was one of those studies where the idea of doing really basic, exploratory science shines," he says.

His lab works with C. elegans, a transparent (and not parasitic) nematode, usually about a millimeter long with about 3,000 cells. Probably somewhat disappointing to humans, its genome is similar to us.

Fay, MCLS doctorate student Melissa Kelley and others in his lab found themselves looking at a mutant that had an unusual phenotype, one not well described or understood at any level.

"Some of the fun of it is like sleuthing, figuring out what happened," says Fay, flashing that look.

They solved the mystery of the mutant phenotype in good detail. In this case, it led to genes conserved in humans.

"Thanks to previous studies from another group, we already knew that genes with clear human correlates were involved in what we were studying," Fay says. "That's partially what made us interested in the problem to begin with. We knew the study would have relevance to human biology and possibly disease."

Their research led to a gene that encodes a worm protein related to the

fibrillin proteins in humans. Fibrillins are essential for proper formation and function of elastic-like fibers in connective tissues. Fibrillin works outside the cell, providing structural support—a scaffold—for the cell.

Two of the three fibrillin proteins in humans are associated with disease—in particular, Marfan syndrome. Marfan affects connective tissues, and symptoms can be long arms, legs and fingers, a tall and thin body type, flat feet, and harder-to-detect signs such as aorta defects. Some have speculated Abraham Lincoln had the syndrome, but many now reject that.

The lab's mutant worm didn't have a normal scaffolding system. This led to a range of deformities in the developing worms, Fay says, and the discovery of certain intrinsic biomechanical forces operating in embryos that no one had previously theorized.

Results were first published March 13 in eLife, a highly regarded open-access scientific journal. Publication in eLife is free because of backing by the Howard Hughes, Max Plank and Wellcome Trust Institutes. The Fay lab is the first from UW to publish an article in the journal.

Fay credits his collaborators, including Nobel Laureate Martin Chalfie in the Department of Biological Sciences at Columbia University. Others are from Stanford University, Universidad Mayor, Harvard Medical School, Rockefeller University and the David Geffen School of Medicine at UCLA.

Kelley is one of three lead authors.

"I have been very fortunate with this project, both to be able to work on well-established research, and because I have had this opportunity to be an author on a paper with such outstanding collaborators," says Kelley, who is interested in studying developmental biology and human diseases.

More information: "FBN-1, a fibrillin-related protein, is required for resistance of the epidermis to mechanical deformation during C. elegans embryogenesis." *eLife* 2015;4:e06565 DOI: dx.doi.org/10.7554/eLife.06565

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