PROFILES

How Helen Willsey broke new ground, frogs in hand

BY **GRACE HUCKINS**

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The night before her first talk in graduate school, **Helen Willsey** was curled up on the floor of a meeting room, her then-boyfriend struggling to console her. It was the early 2010s, and Willsey was working on a Ph.D. in genetics at Yale University. She was terrified that her audience would see the data she had produced and deem her inadequate, someone who didn't belong in the exalted halls of science.

Few other aspects of science perturbed her — from keeping fly colonies healthy to looking at their tiny wings under a microscope or dreaming up new experiments to probe unsolved questions, she was invested and motivated. But back then, Willsey faced every talk, paper submission and grant application with near-crippling trepidation. No matter how strongly she believed in her own ideas, she dreaded the prospect of being judged by a community that might find her skills lacking.

So, to get through that talk and the scores of talks that succeeded it, Willsey pretended. She had been an avid performer since childhood; she had danced nearly her whole life, and she acted in several musicals as an undergraduate student at Duke University in Durham, North Carolina. She realized giving a talk could be like playing a character on stage: She could pull on her blazer like she was putting on a theatrical costume and transform into someone unafraid of being judged. That way, her audience would see only the confident scientist she was pretending to be.

Willsey grew up the youngest of seven; neither of her parents had siblings, and they wanted to have a lot of children. In such a large family, Willsey quickly learned that if she wanted something done, she would have to do it herself. At age 3, frustrated about sharing a bedroom with her brother, she took it upon herself to convert a closet into her own bedroom — and then slept in it for years.

In her third year of high school in Nashville, Tennessee, Willsey got her first taste of scientific research during a two-week internship in the lab of **Marshall Summar**, a molecular geneticist who studies rare diseases in children. But she didn't decide to become a scientist until she learned in an undergraduate biology class about the Nobel Prize-winning work of **Christiane Nüsslein-Volhard** and **Eric Wieschaus**, who used a mutagenic screen in fruit flies to discover a series of genes that govern embryonic development. The clear line between individual gene mutations and associated phenotypes fascinated her, as did the idea that the lowly fly could help solve some of the mysteries of human biology.

Her interest piqued, Willsey thought at first that she might pursue an M.D./Ph.D. — she loved science, and she was motivated to help people. But when she tried shadowing doctors at local hospitals, she struggled to handle what she was seeing. "It was too much," she says. "I was too emotionally pulled by it."

By electing to become a researcher, Willsey could keep a comfortable distance from human suffering while still working to alleviate it. And the life of a scientist suited her: Willsey loved the fly research she did as a graduate student, flipping her stocks daily, mating virgin animals and observing the phenotypes she generated. But as the end of her Ph.D. edged closer, she wasn't sure what direction she wanted her research to take next — until she heard **Matthew State**, professor of psychiatry at the University of California, San Francisco, give a talk about identifying some of the first **high-confidence de novo mutations** associated with autism. "They weren't things that made a lot of sense," Willsey says. The mutations affected proteins that took care of generic things within the cell, such as cutting microtubules and binding to the regulatory protein ubiquitin. None of it was obviously linked to autism, and that mystery compelled her. "To see such a broad, functional categorization of these genes was intriguing to me."

> "I was just eviscerated. And that pissed me off, because the ideas for the fellowships were good." Helen Willsey

She considered trying to study those genes in flies but wanted to use an organism that better modeled human development — a vertebrate, with a more human-like genome. Mice, one of the workhorses of autism research, were an option, but Willsey wanted to study multiple genes at once, and mice reproduce too slowly to make that possible.

The solution that she arrived at was ***Xenopus tropicalis***, a small frog native to West Africa. Though less well known than fruit flies and zebrafish, *Xenopus* has an illustrious history in biological research: The first pregnancy test involved injecting a potentially pregnant person's urine into another species of *Xenopus* to see if the frog would release eggs. If injected with human chorionic gonadotropin, an adult female *Xenopus* will produce thousands of eggs, which can then be fertilized using testes harvested from *Xenopus* males.

But in 2015, with her Ph.D. all but completed, Willsey had little idea how to do any of this. So she enrolled in Cold Spring Harbor Laboratory's Cell & Developmental Biology of *Xenopus* course, where she spent two weeks, night and day, learning the scientific and animal husbandry tools she would need for her research. She was so determined to complete the course that she took only 12 hours off to return to Yale to defend her dissertation. Her excitement about frog work "actually made it a lot easier to say goodbye to graduate school," she says.

But Willsey still had one problem: She had yet to publish an academic paper.

Willsey applied for several postdoctoral fellowships while trying to publish her doctoral research, and she was rejected from every single one. "I was just eviscerated," she says. "And that pissed me off, because the ideas for the fellowships were good."

Eventually, she found a position working with **Richard Harland**, professor of genetics at the University of California, Berkeley, who is a preeminent *Xenopus* expert. Because she did not have her own funding, she was dependent on Harland for financial support, and after a year in his lab she had to move on. By this point, she had **published** her Ph.D. research on flies, but her core idea — that autism-linked genes could be studied in *Xenopus tropicalis* — remained untested and unproven. When she made small talk about her work at conferences, she was met with a persistent drumbeat of skepticism.

To convince the doubters, she needed results; and to obtain results, she needed funding. That's when she reconnected with State. She pitched her idea, and State — in about five minutes, he says — saw its promise and offered her a place in his lab, with all the funding and resources that entailed.

But State isn't a frog scientist. He could give Willsey the money she needed to get her work going and advise her on autism genetics, but she was on her own when it came to the frogs. While everyone else in State's lab was running PCRs and sending off DNA samples to be sequenced, Willsey was ordering frogs and tanks and scrambling to find a room to house them.

She had few other options. If she wanted to use *Xenopus* to study autism, she had to prove that it could work — and obtaining that proof would take a lot of troubleshooting, tinkering and long nights at the bench. For five years she toiled single-mindedly in State's lab, seeking the results that would demonstrate, once and for all, that she was right and the skeptics had been wrong. She knew what she was doing was great. If anyone else couldn't see it, she figured, they were closed-minded.

In graduate school, Willsey had dealt with negative feedback from colleagues or peers by spending time alone in the lab, picking the virgin flies out of her stocks — a repetitive task that allowed her mind to wander toward whatever intellectual tangle she was working to resolve. When she transitioned to frogs, she began to find that same solace in microscopy, adjusting staining procedures and instrument settings until she could capture an image that, in one fell swoop, told the story of a particular gene.

To tell those stories, Willsey leveraged a quirk of *Xenopus* biology that allows a single frog to effectively serve as its own control in a genetics experiment. At the two-cell embryonic stage, one of the cells is destined to become the left half of the frog's body, and the other, the right. By injecting a CRISPR editing molecule into one cell and not the other, Willsey could mutate one half of a frog while leaving the other untouched. This approach enabled her to observe effects that would otherwise have been undetectable. If a mutant frog has a slightly bigger or slightly smaller brain than a control animal, for example, it's difficult to attribute that effect to the mutation, because some animals are just naturally bigger than others. But when one half of an animal's brain is bigger than the other, the effect is obvious.

> "You have to be kind of fearless to take frogs into the autism world." Matthew State

But that wasn't the most important advantage that *Xenopus* offered Willsey. When she made the decision to pursue autism genetics, she realized she could make the most progress not by looking at risk genes individually, but by examining many in parallel. "If you study just one gene, there may be five different things it does, and on its own it's hard to know which, if any, of those things are actually relevant to autism," she says. By investigating the role of multiple autism-linked mutations in the same model organism and directly comparing the resulting phenotypes, Willsey could pinpoint their effects. Many of the genes Willsey studied had previously been thought to **play their primary role at the synapse**, but studying those genes in developing *Xenopus*, where they had never been examined before, enabled Willsey to highlight an atypical role for those genes — and to link that role to autism.

In a **single paper**, Willsey covered 10 different high-confidence autism-linked genes. And by CRISPR editing only half of each frog, she could observe that every one of those genes made the mutated half of the brain either bigger or smaller than the corresponding control half. On further examination, she discovered that the mutant half of every frog displayed abnormally high numbers of neural progenitor cells, indicating that something was going wrong in the process of neurogenesis.

Early in 2021, she published those results in *Neuron*. With that paper, Willsey at last had evidence that her research plan worked. She was hired at the University of California, San Francisco, soon after.

Before Willsey, no one had ever used frogs to study autism. To pursue it took not only obstinance, but guts. “You have to be kind of fearless to take frogs into the autism world,” State says. “That’s what ends up really moving the field forward.”

In September 2021, Willsey started her role as assistant professor of psychiatry. Her **lab space** used to be part of State’s laboratory — it’s the same place she worked when she was a postdoc running her own mini-lab — but it clearly belongs to Willsey now. To keep light from getting into the microscope room, she has hung a large, multicolored flag with a grinning cartoon frog and a slogan boldly lettered in yellow: “Welcome to the pad.”

“The frog flag was one of the first things I put up when it was just me,” she says.

She recognizes that scientific success is, to a certain extent, a crapshoot, and she thinks her greatest impact could well take place within the walls of her lab. Willsey won the university’s Dean’s Award for Excellence in Mentoring in 2020 when she was still working with State, and she remains a committed mentor now that she has her own team. “The thing that will always return in spades, and I know will be a positive impact no matter what, is taking care of these people and watching them grow, and seeing them progress,” she says.

Willsey’s group is still relatively small — one postdoctoral fellow, one graduate student, three research assistants, an undergraduate student and a high schooler. And last summer, she welcomed two more high school students, much like Summar welcomed her almost two decades ago. Willsey makes it a point to give all of these lab members — including the high schoolers — the opportunity to present to the rest of the team during their time in the lab, if they want to. She wants her mentees to be able to practice that skill somewhere safe and friendly before they have to get up before a critical audience.

Willsey is now married to the boyfriend who consoled her when she struggled with presentation anxiety in graduate school, and they have two children. She often Facetimes them while she’s at the lab. Her daughter, Willsey says, doesn’t yet understand the idea of a ‘student,’ so she calls the lab members Willsey’s friends — indeed, **Micaela Lasser**, Willsey’s postdoc, says that coming into the lab feels like hanging out with a bunch of friends who all love science. Lasser had an offer to postdoc in a more established lab, but she chose Willsey. “When you find an environment like that, you go for it,” Lasser says.

Soon, the Willsey lab will move to a new building, where Willsey will be able to keep far more frogs and worry a lot less about the day-to-day tasks of keeping them alive. After laboring for years to prove that her ideas held water, she now has a *Neuron* paper, a tenure-track job, and $1 million of no-strings-attached funding from the **Chan Zuckerberg Biohub**.

It’s no coincidence that Willsey recently gave her first truly comfortable talk to her funders, who had already expressed their faith in her through a major grant. Willsey didn’t have to pretend to belong while giving that talk — she had concrete proof that she did.

She still sometimes struggles with her confidence. But if the past several years have proven anything to her, it’s that her determination to tread new scientific ground, and her love for the sheer act of doing science, can propel her through those moments of uncertainty. “There’s plenty of self-doubt,” she says. “There’s plenty of self-criticism mixed in there, too. But when I see a new idea that I think is exciting, there’s not going to be much that’s going to be able to hold me back.”

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