Profile of Huda Y. Zoghbi

In the fall of 1983, the chance intersection of three events—the publication of a journal article, the visit of a patient to the genetics clinic at Texas Children's Hospital (Houston, TX), and another patient's arrival at the Blue Bird Circle Clinic (Houston, TX)—dramatically changed the life of pediatric neurologist Huda Y. Zoghbi. The common thread of these events was Rett syndrome, a rare, disabling neurodevelopmental disease characterized by loss of speech and constant hand-wringing. That fall, Zoghbi had read the first account of Rett syndrome in an American medical journal (1); within 2 weeks, she encountered two young girls who had the classic symptoms of the disorder. Almost immediately, Zoghbi became an expert on this little-known disease.

These coincidences caught Zoghbi's attention at first, but her desire to help Rett syndrome patients and their families exerted lasting effects on her career. Two years after first encountering patients with this disorder, Zoghbi sidelined her clinical career and formally trained as a researcher in genetics in the hopes of understanding the causes of diseases like Rett syndrome. Nearly 20 years later, in 2004, she was elected to the National Academy of Sciences for her research on the molecular genetics of neurological disorders, including her 1999 discovery of the gene responsible for Rett syndrome. Zoghbi's Inaugural Article (2), published in a recent issue of PNAS, continues her explorations of the disease's mechanisms.

Zoghbi is now a professor in the departments of Pediatrics, Molecular and Human Genetics, and Neurology and Neuroscience at Baylor College of Medicine (Houston, TX), as well as an investigator of the Howard Hughes Medical Institute. Her work has helped uncover genes and mechanisms responsible for not only Rett syndrome but also for spinocerebellar ataxia neurological disorders. Zoghbi's research in animal models of the *Math1* gene, which is important for coordination of the sense of position in space (3–6), has shed light on diverse physiological areas, including balance, deafness, respiration, and intestinal development.

Medical School, No Matter What

Zoghbi was born Huda El-Hibri in Beirut, Lebanon, and spent her teenage years during "Beirut's most wonderful days," she says, in a time of peace and thriving culture. In high school, she fell in love with the literary works of Shakespeare and other English-language poets, and she wanted to study literature at the university. Her mother, who had never attended college, persuaded her to give biology a chance instead. "She, in her wisdom, thought I could always write on the side," says Zoghbi, "but she felt that, especially as a woman growing up in the Middle East, I should pick a career that would ensure independence and security. So I did."

Huda Y. Zoghbi

Zoghbi applied as a biological sciences major to the most competitive university in the Middle East, the American University of Beirut, founded in 1866, and was accepted in 1973. The science courses delighted her with their rigor and intellectual challenge, and in 1975 she entered the American University of Beirut's medical school, the region's sole American medical program.

But civil war broke out in Lebanon 6 months into Zoghbi's first year of medical school. She lived two miles from campus with her family, and, before long, traveling even that short distance became dangerous. "Bombs were falling everywhere in the city. You could be driving on the street, and a bomb would fall right in front of you," she recalls. Zoghbi and her classmates nonetheless decided they wanted to finish the school year. They begged their professors, most of whom lived within a block of campus, to continue teaching classes. "We never missed a day. We are really very grateful to these professors," she says.

The students, 63 in all, camped in the double-walled basement of the medical school building. Zoghbi found a space to sleep in the women's restroom. Each morning, she woke up, washed her face, and walked upstairs to class. At night, the students gathered in the dark to share their life stories. "The whole class bonded together. We were stuck on campus, and there was nothing to do but talk about our own lives and the future. We are all still very close," she says. It was in this tightly knit medical school class that Zoghbi met her future husband.

Facing Challenges, Yielding to Logic

Zoghbi and her classmates struggled to keep up their studies, but they also worried about their families off campus. After part of Zoghbi's house was damaged by bombs and her brother was injured by shrapnel, her parents insisted the family spend the upcoming summer in the United States. They planned to stay with Zoghbi's sister in Texas and return to Lebanon in the fall.

Over the summer, however, the war escalated, and Lebanon's borders closed. By fall, Zoghbi knew that she would have to remain in the United States, even though finding a medical school to accept her as a transfer student would be difficult. Family friends in Nashville, TN, opened their house to Zoghbi and offered to help search for a school. One university rejected Zoghbi's request outright, but Meharry Medical College in Nashville agreed to accept her. With much hard work, Zoghbi caught up to her classmates and made it through the school year. "It was a very tough year," she says. "I was worried about all my family and friends. But it became a milestone. You reflect on it, and you think that, since you survived it, you can handle any other challenges."

The following summer, Zoghbi hoped to return to Lebanon, but her medical school professors in Beirut instead urged her to finish her training in the United States. "They were right. The war was still at its peak, and I didn't see that it would end in a month or two or three. So I yielded to logic and came back," she says. In 1979, Zoghbi finished her training at Meharry Medical College, received her M.D., and joined the Baylor College of Medicine residency program for pediatrics.

Zoghbi planned to specialize in cardiology, but she reconsidered after spending a short rotation in the pediatric neurology clinic at Texas Children's Hospital at the end of her second year of residency. "I became fascinated by the brain, basically," Zoghbi recalls. She found herself attracted to neurology's emphasis on logic and reasoning, where

This is a Profile of a recently elected member of the National Academy of Sciences to accompany the member's Inaugural Article on page 17551 in issue 49 of volume 102.

a thorough patient interview could often lead to the correct diagnosis, regardless of medical tests.

After finishing her final year of residency as chief resident of pediatrics, Zoghbi switched her specialization from cardiology to neurology. The next summer, she married William Zoghbi, her medical school sweetheart from Beirut. William transferred to Meharry Medical College a year after Zoghbi did, and they both then moved to Baylor. In 1982, Zoghbi began a 3-year joint residency/fellowship in pediatric neurology at Baylor.

Hand-Wringing Clues

In 1983, Zoghbi read Bengt Hagberg's account of Rett syndrome in the *Annals of Neurology* (1). Now known to affect 1 in every 10,000–20,000 females, Rett syndrome at the time was virtually unrecognized by many in neurology. Although this syndrome was first reported on by the Viennese pediatrician Andreas Rett in 1966 (7), Hagberg and his colleagues brought this syndrome to the attention of the neurology community. Hagberg's account allowed Zoghbi to diagnose a 5-year-old patient she encountered at Texas Children's Hospital.

Zoghbi learned that this girl had been born apparently healthy and had begun to walk, speak, and interact socially. Then, by her third birthday, everything changed, Zoghbi says. The girl's gait became uncoordinated, her balance suffered, and her head stopped growing normally. She eventually stopped speaking entirely and began wringing her hands constantly. "It was a devastating experience for her young parents," Zoghbi says.

A week later, at the Blue Bird Circle Clinic, Zoghbi saw an 11-year-old patient with the same set of symptoms. "I immediately recognized it is the same syndrome, because how often are you going to see a child wringing her hands constantly?" Zoghbi says. She instructed the clinic's volunteers to look through stacks of medical charts in search of girls with key features of Rett syndrome. Sifting through 30 "candidate" records, she found five more patients, all of whom had been misdiagnosed (8). "So, within 10 days, I went from having never seen a Rett syndrome patient to now [being] one of the newest experts on Rett syndrome," says Zoghbi.

Empathy and Eagerness for Research

Zoghbi became intrigued by the disease's strange progression. Rett syndrome patients are healthy for 1 or 2 years, then deteriorate before stabilizing again—an unusual pattern in neurological disorders. To investigate, Zoghbi started a clinical research project measuring metabolites in spinal fluid of patients with Rett syndrome (8). After these results showed no immediately promising leads, Zoghbi decided to collect DNA samples in the hopes of studying the syndrome from a genetic perspective. At the time, however, she had no experience working with DNA.

Dr. Zoghbi (right) with Ashley Fry, her first patient with Rett syndrome.

"I realized quickly that if I was going to solve the problem I had better go get trained in research," Zoghbi says. She felt torn, because she was eager to begin her medical career, and she knew she would enjoy working as a pediatric neurologist. On the other hand, she had always been frustrated at having to inform parents of their children's neurological disorders without being able to provide consolation, either through concrete medical explanations or through treatments.

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Then, in 1985, Zoghbi gave birth to her first child, which increased her feelings of empathy with parents of children she treated. When her daughter was 4 months old, Zoghbi decided to acquire formal research training in molecular genetics, with an eye toward eventually understanding Rett syndrome. She started work at Baylor College of Medicine with Arthur Beaudet, who accepted her into his laboratory although she lacked research experience. "Eagerness—that's all I had. I was motivated and eager," says Zoghbi.

The Little Gene That Could

Although Rett syndrome was the reason Zoghbi had turned to research, too little data existed for her to begin her new career based on this disease. She instead chose to focus on spinocerebellar ataxia type 1 (SCA1), a fatal, progressive, neurodegenerative disorder affecting balance and coordination. She studied with Beaudet for 3 years, taking graduate courses and doing a postdoctoral fellowship simultaneously.

In 1988, Zoghbi set up her own laboratory at Baylor College of Medicine and continued to collect data on patients with SCA1 around the United States. She collaborated with Harry Orr at the University of Minnesota (Minneapolis, MN), freely sharing data and results. On the same day in 1993, each separately found the gene for SCA1 (9). Zoghbi and Orr learned that the mutation responsible for SCA1 is an expansion of a CAG trinucleotide repeat encoding glutamine, with the size of the repeat inversely correlated with the age of onset of the disease (9). Further work by Zoghbi, Orr, and colleagues revealed the role of protein misfolding and degradation in SCA1, a finding that has proved relevant to other neurodegenerative disorders (10). Current efforts by Zoghbi's group include translating these discoveries into pharmacological interventions, first through trials in mice (11, 12).

After identifying the SCA1 gene, Zoghbi adopted an animal research approach to investigate the genetics of balance. She studied the mammalian homolog of the gene *atonal* based on Baylor colleague Hugo Bellen's explanation about the role of this gene in balance and coordination in fruit flies (13). In 1996, a member of her laboratory cloned its mouse homolog, *Math1*, which turned out to be more productive than Zoghbi had anticipated. Investigations in her laboratory and elsewhere have revealed that *Math1* is essential not only for balance and coordination but also for hearing, newborn breathing, and intestinal functioning (3–6). "We call it 'the little gene that could.' It's a small gene, but it really has essential functions," she says. Currently, Zoghbi's group is interested in pinpointing the role of *Math1* in the network of balance and coordination, especially as it relates to respiration and, potentially, sudden infant death syndrome (14).

Return to Rett

Throughout her career, Zoghbi never forgot the disease that brought her to research in the first place. Her motivations were personal, however, because the scientific community was not encouraging. Colleagues, reviewers, and funding agencies lacked enthusiasm for research on Rett syndrome, in part because few individuals and even fewer families were available for study. "In fact, it was so challenging that I stopped telling anybody I'm working on Rett syndrome after a while, because I felt people would say that I'm just wasting my time," Zoghbi recalls.

Zoghbi never dropped Rett syndrome altogether, however. "Very quietly, I continued to work on it," she says. By 1997, three Rett syndrome families had been identified and studied by Zoghbi, Carolyn Schannen, and Uta Francke, her collaborators at Stanford University (Stanford, CA). In 1999, Zoghbi's group found the Rett syndrome gene, *MECP2* (15). By then, 16 years had passed since Zoghbi first encountered Rett syndrome, and she was finally able to return to her original patients and study their mutations in *MECP2*.

Zoghbi and her colleagues also looked for *MECP2* mutations in other neurologically impaired patients, which yielded surprising results. "Mutations in this gene cause a lot more than Rett syndrome," Zoghbi says. More subtle phenotypes, such as learning disabilities, mental retardation, and autistic spectrum disorders, can be caused by mutations in this gene, depending on how many of the patient's cells express the normal versus mutant allele (16).

Zoghbi's efforts turned to understanding the role of the protein encoded by *MECP2*, and her PNAS Inaugural Article (2) continues this work. "We set out to see if there are any other functions to this protein. We were able to find a protein that interacts with *MECP2* in cells," she says. Zoghbi and her coauthors realized that this protein affects RNA splicing, which led them to discover that *MECP2* itself also can affect RNA splicing. Her group's current efforts in Rett syndrome extend in two directions: defining the neurons in which each of the syndrome's symptoms originated and identifying potential points of intervention that can be pharmacologically manipulated in Rett syndrome mice (17).

A Career Falling into Place

Zoghbi admits that her daily schedule, with her laboratory, patients, and family, is filled to the brim. But for her it is a magical combination of exciting discoveries, supportive relationships with colleagues, and a meaningful cause to strive for. "There's the excitement of coming in every day to find new discoveries, new things that might further the cause you're working on," Zoghbi says. She is hardly alone in these pursuits, she points out, as she enjoys close collaborations with colleagues and mentoring members of her laboratory in their research endeavors. And she keeps in touch with patients and families she has worked with over the years.

Zoghbi's two children and her husband have been boundlessly supportive along the way, she says, allowing her to integrate her work with her family. Everything adds up to a career about which she is wholly passionate. "To me, a scientific career is so thrilling," she says. "The key thing is that if you love what you do it all falls into place. It really doesn't seem like work anymore."

Regina Nuzzo, *Science Writer*

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