Stephen T. Warren 1953–2021

Stephen T. Warren was a key contributor to the 1991 discovery of an unstable trinucleotide repeat that expands in families and causes loss of function in fragile X syndrome.

Steve's deep knowledge of human genetics and his clever insights into somatic cell genetic approaches to isolate cytogenetically detected sites of chromosome instability allowed for identification of *FMR1* and its CGG repeat expansion. One of my great joys in science was working with Steve and our consortium of investigators to understand how repeat length predicts the likelihood of expansion of premutation alleles to full mutations that cause loss of *FMR1* function in families carrying this most common inherited form of intellectual disability and autism. It has been my delight to call Steve a close friend through almost my entire career, while we worked together to understand this and other human genetic disorders. It is with great sadness that I report Steve's death on 6 June 2021, after a short illness. He was 67.

Steve developed an interest in human genetics very early. Born in Detroit in 1953, he enrolled as a zoology major at Michigan State University. Steve became a member of the American Society of Human Genetics (ASHG) and attended his first conference in 1975 as an undergraduate, beginning a long unbroken string of meetings. He spent summers at Henry Ford Hospital in Detroit, learning clinical genetics and seeing patients. By the time he graduated in 1976, Steve had taken all the graduate-level genetics courses, thus making his choice to stay at Michigan State University for his PhD studies an easy one. Steve's work with James Trosko characterized the high rates of mutation in cells derived from people with Bloom syndrome. He published a dozen papers as a graduate student. He met his wife, Karen, in his undergraduate genetics research lab; she went on to Wayne State University Medical School.

Steve joined the lab of Richard Davidson as a postdoctoral fellow at the University of Illinois in Chicago in 1981, while Karen was a resident in internal medicine. Davidson's group was developing somatic cell hybrids, a technique for assigning genes to chromosomes and developing reagents for genome mapping. I became aware of Steve's work while I was engaged in similar studies as a graduate student. We both attended the seminal Somatic Cell Genetics conferences of the Federation of American Societies for Experimental Biology (FASEB) in the early 1980s, where progress in these and other

Stephen T. Warren in his office at Emory University in December 2018, on the occasion of an invited lecture by Huda Zoghbi in honor of his 65th birthday. Credit: David L. Nelson

methods of gene analysis and transfer was presented, but we did not meet formally until 1988, at the first Cold Spring Harbor Genome Mapping and Sequencing meeting. Our parallel journeys and common interest in X-linked mutations provided a strong foundation for our friendship. By 1985, Steve had accepted an assistant professor position in biochemistry at the Emory University School of Medicine in Atlanta.

Steve was using somatic cell hybrids to identify the site of chromosomal fragility at Xq27.3 exhibited by cells from people with fragile X syndrome (FXS). He created hybrid cell lines that retained the X chromosome from people with FXS in rodent cells. Steve developed a panel of hybrid cell lines with breakpoints at the fragile X site, as featured on the cover of *Science* in 1987. Steve's panels were crucial reagents for mapping DNA fragments near the site and ultimately for confirming the isolation of clones containing the region. Steve and I began working together, using yeast artificial chromosomes to identify clones from the region near the fragile site. Together with my postdoctoral mentor C. Thomas Caskey at Baylor College of Medicine and Ben Oostra at Erasmus Medical Center in Rotterdam, we were able to identify clones containing the fragile site and to demonstrate the instability of the region in families. The sequence revealed CGG repeats at the junction and a gene that we termed *FMR1*. After an intense several months of our three groups working around the clock, we published our results in *Cell* on May 31, 1991. Back-to-back papers published a week earlier in *Science* by the groups of Jean-Louis Mandel and Grant Sutherland with Rob Richards also defined the unstable nature of the sequences at the fragile site in FXS families. All groups made use of Steve's hybrid cell lines for mapping, and Steve was also an author on discovery papers from the Australian group; he was very generous with his reagents. Today, some 60 human loci are known to carry unstable repeats that lead to pathology and deviations from Mendelian genetic expectations, and collectively affect many millions of individuals. Steve frequently pointed out that he expected FXS to remain a singular genetic oddity at the time.

The FXS repeat and gene discovery were just the beginning of a long and very productive series of studies by Steve's group to characterize the genetics of the disorder and the function of *FMR1*. His position in a biochemistry department and his natural aptitude for collaboration produced numerous high-profile studies led by his many trainees, who have gone on to have prominent careers. In just a few years, they demonstrated the importance of AGG interruptions in limiting the instability of the CGG repeat, characterized the mechanism of *FMR1* downregulation by the full mutation, demonstrated that *FMR1* encodes a selective RNA-binding protein, identified target mRNAs, characterized signaling properties of the protein and ribosome association, and showed that repeat-bearing *FMR1* mRNA is not well translated. Steve was promoted to professor, was invited to join the Howard Hughes Medical Institute and in 1999 was awarded ASHG's prestigious Allan Award. He was a highly sought-after guest lecturer.

For several years after the identification of *FMR1*, Steve and I often lamented the lack of interest by the neuroscience

community. Steve's efforts through numerous venues helped *FMR1* catch the attention of neuroscientists. Along with the FRAXA Research Foundation, Steve was a key contributor to the development of a decade-long series of small conferences at Cold Spring Harbor Laboratory's Banbury Center, which were aimed at understanding *FMR1* and the consequences of its absence. These meetings elevated the visibility of the disorder and helped move attention toward clinical application. With Kim Huber and Mark Bear, Steve helped develop the mGluR theory of FXS, which stimulated major translational efforts. Steve's welcoming and collaborative approach to new entrants to the field strongly furthered research and set a tone for investigators to follow. Steve continued to contribute to research not only on FXS but also on other human genetic disorders, especially schizophrenia more recently.

Recognizing the maturity of the subject, Steve founded Emory's Department of Human Genetics and served as chair until last year. He built a very successful department that includes a substantial clinical component aimed at both diagnostics and therapeutics. Steve served ASHG as president, board member and editor in chief of its journal. He was also honored by the American Association for the Advancement of Science as a fellow and by the American Academy of Arts and Sciences, and was elected to both the National Academy of Medicine and the National Academy of Sciences. He received the March of Dimes Colonel Harland Sanders Award for lifetime achievement and was named to the Hall of Honor by the National Institute of Child Health and Human Development of the US National Institutes of Health.

Steve was an avid boatsman. He often recalled his delight in sailing on Lake Michigan during his time in Chicago. In Atlanta, he kept a boat on Lake Lanier. He enjoyed taking friends and colleagues out, and departmental retreats at the lake offered that opportunity. In the winter of 2002, Steve slipped on ice on the boat dock and broke his lower leg. His recovery was slow despite extensive physical therapy. Travel became increasingly difficult, but he continued to attend conferences, accept lecture invitations, and serve on advisory and review committees until 2014. In 2015, Steve learned that he had inherited an expanded repeat that explained his slow recovery and diminishing leg strength. Steve was diagnosed with myotonic muscular dystrophy type 2 (DM2), resulting from a tetranucleotide repeat expansion. Steve noted the irony of having discovered the repeat expansion in FXS while having inherited the DM2 expansion. He accepted his limitations with grace and courage, turning his energy to his department. He used the latest devices to assist with his mobility, which allowed him to carry on and participate in life. He closed his lab but continued his work as an associate editor for the *Proceedings of the National Academy of Sciences* and contributed to grant applications, including a recently successful Fragile X Center award that we share.

Missing seeing Steve at conferences, his friends, colleagues and former trainees scheduled more frequent visits to Atlanta. Organized by Steve's long-time assistant, Janelle Clark, a symposium at Emory in the fall of 2016 marked the 25th anniversary of the identification of *FMR1* and included presentations from numerous colleagues. Several continued a tradition of visiting with Steve at least annually until the pandemic intervened. Even then, Janelle organized a virtual birthday celebration last fall. Steve formally stepped down as chair but continued to be an important advisor for his able successor, Peng Jin, this past year. Steve participated actively in a Fragile X Centers virtual meeting just 2 weeks before he became ill. News of his death came as an enormous surprise to us all.

Losing Steve Warren leaves our field greatly diminished. His many friends, collaborators and trainees mourn this loss. We send our deep condolences to Karen and their son, Thomas. Steve touched numerous lives directly through his research as well as through his efforts to enhance training and education. He also reached many beyond his close sphere through the strong example that he set as a researcher and mentor who took rigorous approaches to challenging problems. We pledge to honor his life and legacy by continuing the work he began, seeking to understand genetic contributions to human disease and using the many tools now available to develop effective therapies. We can only hope to emulate Steve's wise and gracious nature. ❐

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