VIEWPOINT

Remembering Steve Warren (1953-2021): A giant in the field of genetics

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Steve Warren, a giant in the field of human genetics, died in June at age 67. In the realm of autism research, he may be best known for having co-discovered the gene **FMR1**, mutations in which cause **fragile X syndrome**, a leading inherited cause of intellectual disability and autism.

Before the human genome was mapped, identifying a disease gene was a major undertaking into the unknown. In the case of FMR1, this painstaking process took nearly half a century.

Scientists first described fragile X syndrome in 1943 and observed its characteristic constriction near the end of the X chromosome's long arm in 1969. By 1991, Steve and his collaborators had pinpointed the gene associated with this fragile site.

Steve's lab had previously used a cumbersome technique called somatic cell hybridization, which involved fusing blood cells from a person with fragile X to rodent cells in culture dishes. They then treated the cells with reagents that **induced translocations** between the human and rodent chromosomes at the fragile X site. By cleverly tracking the genes lost on either side of the fragile X site in different cells, they had identified chromosomal region Xq27.3 as its location.

They then acquired DNA pieces that spanned the fragile X site and rearrangements in the hybrid cell lines, providing the precise address for the fragile X candidate gene, **which they named FMR1**. This crucial step also enabled the team to discover that repeats of the DNA 'letters' CGG in the gene cause fragile X syndrome. The size of this trinucleotide repeat expansion can increase over generations, and having more than 200 CGG repeats silences the FMR1 gene.

The same genetic mechanism has turned out to be relevant to multiple conditions, such as Huntington's disease and several ataxias. And it explains the phenomenon of genetic anticipation: the observation that certain heritable conditions present more severely in later generations. Until the discovery of the repeat-expansion process, some textbooks dismissed the idea of genetic anticipation as a mere artifact of ascertainment bias — that is, that the symptoms of a heritable disease appear more obvious once one knows that the members of a particular family are at high risk for those symptoms.

For these and other discoveries, Steve received the William Allan Award from the American Society of Human Genetics, the organization's highest honor. In 2001, he founded Emory University's Department of Human Genetics, which he chaired until 2020. His scientific intellect and generosity are sorely missed.

Here we share our individual reflections about Steve:

Joseph Cubells: I first met Steve in 2003, when I had the privilege of traveling to Emory to present my work on the genetics regulating the activity of an enzyme called dopamine-beta-hydroxylase in human serum. After I met with Steve, and subsequently with Charlie Nemeroff, then the chair of psychiatry and behavioral sciences at Emory, Steve and Charlie decided to recruit me to Emory from Yale.

How many chairs of human genetics do you know who would recruit a psychiatrist to take a primary appointment in his or her department? Perhaps Steve liked the idea of a psychiatrist trying to understand the role of a single gene product in complex behavioral differences — after all, that is what he and his colleagues did in discovering and elucidating the molecular basis of fragile X syndrome.

Something that always stood out about Steve was his deep conviction that pursuing high-quality basic research is ultimately the most successful path to helping patients. He once pointed out to me that a single key scientific discovery could help many more patients than the efforts of even the most talented and dedicated individual clinician. That thirst to understand human disorders at their most fundamental molecular levels clearly drove Steve. What an inspiration he was to us all.

First and foremost, Steve was a brilliant scientist — co-discoverer not just of a disease gene, but of a genetic mechanism relevant to multiple disorders.

Steve had other talents that rivaled his powerful intellect and scientific prowess. His leadership skills immediately come to mind in this regard. As chair of human genetics, his desire to maximize the success and opportunities of his faculty was always apparent. I vividly remember my first faculty review meeting with him in 2005. He began the meeting with a simple question that literally reframed the discussion for me and showed me just how great a support he would always be for my professional development. He asked, "How can I be helpful to you?" That question, which

directly conveyed his desire to help every one of his colleagues to excel, embodies how Steve approached his leadership role.

Finally, his personal qualities were remarkable. Born and raised in Detroit, Michigan, he was at his core a practical, honest, idealistic and altruistic Midwesterner. He approached the world with an eye to what was good and wholesome about it. He was always willing to help solve problems and support his faculty even in difficult times, and he always approached challenges in a fair-minded and good-humored way.

A few years back, I struggled through a prolonged period when none of my grant applications succeeded. Steve continued to support me, ensuring that my research time was protected so I could continue to pursue my scientific work and apply for funding. When in 2019 my colleagues and I finally did bring in substantial federal funding (to investigate the physiological and cellular aspects of risk for psychosis in a condition called 22q11 deletion syndrome), Steve was just so excited. I can remember his response to my telling him we had gotten the grant and thanking him for supporting me during lean times: “Joe, that is fantastic news!” He was genuinely thrilled at my success. That was Steve. The most inspiring chair under whom I have served in more than 40 years of working in the world of science.

I know I speak for every single person in my department, whether faculty, staff, student or postdoctoral researcher, when I say we miss him dearly and feel genuinely blessed to have known him.

Evan Eichler: Steve was a de-facto mentor over my entire career. I first met him as a graduate student in David Nelson’s laboratory at Baylor College Medicine in Houston, Texas, in the early 1990s. I arrived in the laboratory shortly after Steve and David had discovered the CGG triplet repeat expansion and its role in fragile X syndrome. Steve and David were close friends, and Steve very quickly became an unofficial mentor of mine who was instrumental in some of my early work as a student. He was sharp and scientifically rigorous, always getting quickly to the heart of the matter, and he was incredibly supportive.

What I remember most about Steve was his encouragement and grace in the face of rejection. When one of my first papers was ultimately rejected from *Science* after a couple of rounds of extensive revision (after Steve assuring me initially that it was a shoo-in), he remained upbeat, reminding me that the paper was still a great piece of work and would ultimately find a great home. His confidence and enthusiasm helped propel me forward and convinced me that I might actually make it as an independent investigator.

Many years later when he offered me a faculty position at Emory, which I ultimately declined, he once again demonstrated this same grace and a knack for uplifting — saying that he hoped that his offer could be leveraged to help me get a position elsewhere. While I didn’t immediately recognize it then, Steve was the epitome of a great mentor, chairman and scientist. He was an inspiration to

so many who worked with him. While his early passing is a loss to the field of human genetics research, I personally will miss his advice, mentorship and friendship much more.

Clockwise from left: David Nelson, Huda Zoghbi, Harry Orr, Janelle Clark, Peng Jin, Steve Warren.

James Sutcliffe: I had the good fortune to be Steve's first graduate student, arriving at Emory in the fall of 1986. Steve was a newly minted assistant professor in the Department of Biochemistry. He was a fantastic mentor, and it was fun being part of that group. Steve's sense of humor was legend, and he loved telling stories. We went on frequent lab lunches and other adventures. I have vivid memories of the first paper we wrote together, and how my tortured first draft came back with so many red editor's marks that the original text was unrecognizable. That experience, though, taught me how to write.

The period leading up to the fragile X site discovery was formative. After a few years of what felt like fumbling in the lab, my experiments began to work, and I felt like I was in command of what I was doing. One day I developed an X-ray film demonstrating how we had cloned the DNA flanking the fragile X site and breakpoints in the somatic cell hybrid lines Steve had developed. Steve was in Rotterdam, the Netherlands, visiting our collaborator, Ben Oostra, so I turned that blot into a figure and faxed it to them in Ben's lab. (This was before email was common.) From that moment until the publication of the fragile X site and gene in *Cell* in 1991, our work was very intense and rewarding.

I also recall preparing my dissertation defense seminar, and how Steve advised me to "tell a story" in that seminar (and in subsequent postdoc interviews). It's such simple advice, but it framed how to think about giving a good talk and was really useful for me at the time. I also remember that Steve had a way of helping others understand how the science world worked, and much of that came from funny stories he would tell about his own experiences. He reveled in the successes of his former trainees, and he really cared to know how you were doing and what was going on in your life

Huda Zoghbi: I got to know Steve through his collaboration with my Baylor colleagues David Nelson and Tom Caskey in their intense efforts to identify the gene behind fragile X syndrome.

Steve was a superb geneticist and biochemist, and he proceeded to study FMR1 and the protein it encodes, FMRP, at every level. His group showed that the large expansions cause a loss of function of the gene, and intermediate repeat expansions drive pathology by a gain-of-function mechanism. They showed that FMRP is an RNA-binding protein that governs the translation of many other proteins. Realizing that the field of neuroscience would both contribute to and learn from studies of fragile X, Steve made a concerted effort to draw neurobiologists as well as RNA

biologists into the fold, particularly at several memorable meetings at the Howard Hughes Medical Institute in Chevy Chase, Maryland. He succeeded, in large part because he set a precedent for generosity in sharing ideas and reagents at a time when the field was extremely competitive and reagents were precious. Fruitful new collaborations revealed that the loss of FMRP leads to excessive glutamate signaling in neurons, paving the way for potential treatments.

Steve's innate, rock-solid decency made him a respected and sought-after colleague. When you were with him, you received his undivided attention. He was an unassuming man who devoted tremendous energy to his work for the good of science. He continually brought out the best in his trainees and colleagues with his fairness, kindness and irresistible joie de vivre. When I served with him and other scientists as peer reviewer of federal grant applications, I looked forward to the meetings he led, because he kept the atmosphere stimulating, engaging and positive in a way that seemed effortless — rarely have I seen a group of tired, overworked scientists so relaxed and happy to be discussing grants! His kindly demeanor complemented a keen scientific mind, and this winning combination made him an effective and well-loved leader, whether in those grant-review panels, the American Society of Human Genetics or his department at Emory.

We will all miss him deeply, but we know his legacy will live on through his trainees and all the fragile X families he has helped through his scientific research, his leadership and his generosity as a human being.

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