PROFILE

Profile of Stephen T. Warren

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In 1991 Stephen Warren, a geneticist who studies certain forms of intellectual disability, and his collaborators identified the gene mutation responsible for fragile X syndrome, a commonly inherited form of cognitive impairment associated with autism. Since then, Warren and his colleagues have continued to study fragile X syndrome, paving the way for the development of drugs to treat the condition. Warren, who is the founding chairman of the department of human genetics at the Emory University School of Medicine, also conducts research on schizophrenia, hoping to identify genes that contribute to this mental disorder. For these and other efforts, Warren was elected in 2011 to the National Academy of Sciences.

Early Resolve for Research

Born in 1953 in East Detroit, Michigan, Warren was his parents' only child. "My father was a dentist and instilled a strong interest in science in me," says Warren. He remembers donning a white medical coat and playing the part of penicillin discoverer Alexander Fleming in a third grade play. Like Fleming, Warren wanted to do medical research and assumed that he would have to become a physician to achieve the goal.

In 1972 Warren began studies at Michigan State University. The same year, he met geneticist James Higgins, who became an early mentor. "Dr. Higgins was one of those individuals with a PhD who was trained in clinical genetics and who routinely saw patients and performed laboratory genetic testing," says Warren.

Higgins introduced Warren to two other clinical geneticists, Lester Weiss and Gene Jackson of Henry Ford Hospital in Detroit, with whom he would work during summer breaks during his undergraduate years. Warren impressed his mentors, who asked him to help establish Detroit's first Tay-Sachs disease screening program. Warren used his own blood serum as the control for the program and returned every year to the hospital to donate blood. Weiss and Jackson encouraged Warren to apply to medical school and allowed Warren to assist in everything from surgery to work in the hospital's emergency room. "Although grateful for the experiences, this only strengthened my resolve for research," Warren says.

Investigation of Bloom Syndrome

After earning a bachelor's degree from Michigan State University in 1976, Warren stayed at the university to pursue a doctorate in human genetics, which he obtained in 1981. "Medical genetics was the perfect fit for me, where I could devote the majority of my time on research but still see patients on occasion for diagnoses and genetic counseling," he says. As a graduate student, Warren worked in pediatric genetics, regularly seeing patients. At Michigan State, he also met his wife Karen, now an internal medicine physician at The Emory Clinic.

Warren at the time conducted extensive research on Bloom syndrome, an inherited disorder. He published 12 papers as a graduate student, including one in which he and his team discovered that cells from patients mutate at high rates, explaining the high cancer incidence in the disorder (1). Warren says his doctoral adviser, James Trosko, provided valuable guidance: "He taught me to think bold thoughts and to take risks in research, as well as not to be intimidated by a new technical area where my research led me."

Hunt for the Fragile X Gene

Warren undertook four years of postdoctoral studies in human molecular genetics at the University of Illinois at Chicago, where he learned about "marker X syndrome," now known as fragile X syndrome. Previous studies determined that fragile X syndrome, like Bloom syndrome, was caused by gene mutations affecting chromosome structure. Unlike Bloom syndrome, which is caused by a genetic defect that results in an increased number of random chromosomal breaks, fragile X breakage occurs on a single locus on the X chromosome. Hence, Warren suspected he could find the gene responsible for fragile X syndrome.

In 1985 Warren joined Emory University as an assistant professor of biochemistry with a joint appointment in the department of pediatrics. The university allowed Warren to devote substantial time to research. He

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gained additional financial support from the Howard Hughes Medical Institute, which helped fund his quest to discover the fragile X gene.

An early effort involved inserting the human fragile X chromosome into a rodent cell line, creating a somatic cell hybrid (2). Warren says, "Prior to the Human Genome Project, cloning disease-causing genes was an exceedingly difficult undertaking that relied on precise mapping of the gene." The somatic cell hybrid enabled the researchers to induce translocations at the "fragile site" on the human X chromosome. Although this was an important first attempt at identifying the fragile X gene, the bacteria in which the human "fragile" DNA was placed were unstable. Warren sought another approach.

Isolation and Analysis of *FMR1*

At a 1989 Cold Spring Harbor Laboratory meeting in New York concerning the human genome project, Warren heard Baylor College postdoctoral fellow David Nelson describe how he and his mentor, Thomas Caskey, used yeast instead of bacteria to clone the human X chromosome. The trio

This is a Profile of a recently elected member of the National Academy of Sciences to accompany the member's Inaugural Article on page 949 in issue 4 of volume 112.

joined forces with an international team that included Erasmus University geneticist Ben Oostra. Warren says, "Using the somatic cell hybrids with translocations described in the prior paper, we ultimately cloned the gene responsible for fragile X syndrome that we called *FMR1* [fragile X mental retardation 1] (3). We also discovered for the first time a trinucleotide repeat mutation where a normal simple repeat in a gene unstably expands upon transmission, disrupting the function of the gene."

Subsequent studies on FMRP, the protein missing in patients with fragile X syndrome, helped determine that FMRP is an RNA-binding protein (4). The work ascribed a potential function for this previously mysterious protein. Warren and his colleagues also found that FMRP associates with polyribosomes (5), affecting the translation of mRNAs involved in fragile X syndrome. Subsequent research discovered that the absence of FMRP leads to overactive signaling and unregulated protein production at synapses (6), in turn leading to structural changes at synapses and an impairment of cells' ability to respond to chemical signals and interfering with learning and memory.

In recognition of this and other achievements, Warren won the William Allen Award from The American Society of Human Genetics in 1999. The same year he began work as editor-in-chief of *The American Journal of Human Genetics*, a position that he held until 2005.

Identifying Treatments for Fragile X

Over the past decade, most research on FMRP has focused on the protein's ability to selectively bind mRNAs and control their translation in postsynaptic neurons, or dendrites. Warren's Inaugural Article (7) describes a fragile X patient with a rare mutation in which a single nucleotide change results in a codon that codes for a different amino acid. "We show that all known postsynaptic functions relating to translation appear to be intact, but a presynaptic function of FMRP, recently shown to include the modulation of action potential duration, is disrupted," Warren says. FMRP therefore appears to have two independent functions.

Warren's work on fragile X is helping to identify potential treatments for the disorder. In 2004, the researchers mapped out a strategy for a potential therapeutic intervention by modulation of the synaptic signaling through the glutamate receptor (8). Warren says, "It led to a substantial effort by many investigators to search for a pharmaceutical treatment of this disorder."

Honors followed. In 2004 Warren was elected to the Institute of Medicine. He was also elected president of The American Society of Human Genetics in 2006, and won the Colonel Harland Sanders Award from the March of Dimes in 2011. In 2013 Warren was honored for Excellence in Molecular Diagnostics from the Association of Molecular Pathology.

Bridging the Gap Between Genes and Biology

Warren, who is currently the William Patterson Timmie Professor of Human Genetics and the Charles Howard Candler Chair in Human Genetics at the Emory University School of Medicine, maintains an active research program on fragile X syndrome and *FMR1*-associated diseases. He and his colleagues are particularly interested in using whole-genome sequencing to identify modifier genes that affect comorbid phenotypes. Mutation of *FMR1*, for example, not only causes fragile X syndrome, but is also linked to fragile X tremor/ataxia syndrome, or FXTAS. This disorder usually affects adult males and may result in Parkinson-like symptoms as well as cognitive decline.

Warren and his collaborators recently initiated a research effort on schizophrenia, seeking loci on the genome that predispose certain individuals to the disorder. One effort is to perform whole-genome sequencing in patients with 22q11.2 deletion syndrome, where nearly a third of the patients will develop schizophrenia. Warren says, "Understanding genome variation that either causes disease or predisposes to disease is the initial toehold for the long climb in understanding the pathophysiology of the disease and, ultimately, therapeutic approaches."

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