2019 Victor A. McKusick Leadership Award[1]

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Thank you, David, for the kind introduction. I am honored to receive an award bearing the name of Victor McKusick, one of my heroes in genetics, and to join the ranks of the distinguished previous awardees who have inspired me in my career. I thank the board and the selection committee. Most importantly, I thank my patients and their families for their trust and support. Over the next few minutes, I would like to share with you why I love genetics and believe it holds the secrets to advancing medicine and health.

My life has been punctuated by remarkable chance events and incredible people. I began medical school at the American University of Beirut, but the Lebanese civil war led me to complete my degree at Meharry Medical College, thanks to the intervention of the dean who allowed me to transfer mid-semester. Although I had excellent grades, most residency programs passed over my application. Once again, my fate hinged on one special person: during a rotation at Baylor, I met Ralph Feigin, the chair of pediatrics, who expressed real interest in me, and on Match Day, learned that I would be in Houston. Ralph taught me not to overlook any clinical detail and to master the literature. I'd intended to pursue pediatric cardiology, but when I rotated in neurology under Marvin Fishman, I was inspired to become a neurologist.

My career path changed again when, as resident, I met a girl named Ashley who had been healthy until she turned two. Then, over a period of a few weeks, she stopped speaking and gradually lost all the milestones she had achieved. She withdrew from her parents and spent hours wringing her hands. Ashley was referred by her pediatrician, who suspected Rett syndrome based on a paper just published by Bengt Hagberg, describing the syndrome for the first time in English. I saw Ashley with Alan Percy and Vincent Riccardi, the attending neurologist and geneticist. I was intrigued by Ashley's diagnosis, but a serendipitous meeting a week later with a girl diagnosed with cerebral palsy sealed my relationship with Rett syndrome. As she walked into the exam room, wringing her hands, I immediately realized it wasn't cerebral palsy, but Rett syndrome. Combing through the clinic's medical records, I ended up identifying and examining six girls with Rett syndrome within a few weeks. Rett was unlike any other disease I had seen, being neither congenital nor neurodegenerative.

After seeing these girls, I was convinced the cause was genetic and felt compelled to figure it out. I approached Art Beaudet about doing a research fellowship in his lab to learn molecular genetics. Art took me on despite my having no research background whatsoever. I shared my desire to work on Rett, but Art urged me to find a Mendelian disease to study because finding the causal mutation for a sporadic disease with the technology available in 1985 was not possible. Though I kept working on Rett, I took his advice and expressed interest in dominantly inherited neurodegenerative disorders. He introduced me to members of a family with a rare, dominantly inherited ataxia. I traveled to Montgomery, Texas for months to examine the extended family and collect blood for DNA. Art taught me how to do science. He is a dear friend to this day and I remain forever in his debt.

During my efforts mapping the ataxia gene, I read a paper by Harry Orr, describing a family in Minnesota with spinocerebellar ataxia that had its gene localized to chromosome 6—the same chromosome my research had pointed to. Strangely, the genes in our respective families mapped to two different regions of chromosome 6. Back then, there weren't many DNA markers, but the late David Cox had developed radiation hybrids to generate fragments of chromosomes. Under David's guidance over the phone, I learned the protocol and developed radiation hybrids for chromosome 6, which gave me a good excuse to call Harry and offer to collaborate.

[1]This article is based on the address given by the author at the meeting of the American Society of Human Genetics (ASHG) on October 16, 2019, in Houston, Texas. The audio of the original address can be found at the ASHG website; [2]Department of Molecular and Human Genetics, Baylor College of Medicine, Houston TX, 77030, USA; [3]Department of Pediatrics, Baylor College of Medicine, Houston TX, 77030, USA; [4]Department of Neurology, Baylor College of Medicine, Houston TX, 77030, USA; [5]Department of Neuroscience, Baylor College of Medicine, Houston TX, 77030, USA; [6]Jan and Dan Duncan Neurological Research Institute, Texas Children's Hospital, Houston, TX 77030, USA; [7]Howard Hughes Medical Institute, Chevy Chase, MD 20815, USA
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To my delight, Harry agreed to collaborate. We worked together on our different regions of chromosome 6, but it bothered me that the same clinical entity could map to two different regions of the same chromosome. (This would not seem strange today, given our knowledge of genetic heterogeneity.) I did a lot of detective work and figured out that in a small branch of the Texas family, the disease did not come from the main bloodline but from a spouse who died before developing symptoms. The odds of a disease with a prevalence of 1/100,000 to run in the same family through two unrelated bloodlines were unfathomable, but it happened. I realized that by including this individual, my gene mapped on top of the gene in Harry's family.

Between 1988 and 1993, we continued marching through genes. David Nelson and I had many discussions about the CGG repeat expansion causing Fragile X syndrome, but I never suspected any connection with SCA1. But one day, Tom Caskey, then-chair of genetics at Baylor, gave a seminar about CTG expansion causing myotonic dystrophy. He described how the repeat expansion explained anticipation, the worsening of the disease as it passes through generations, and I realized this was exactly what I was seeing in my SCA1 family. I called Harry, and we agreed to divide the million-base-pair candidate region between us and search for triplet repeats. We also agreed that we would both cover a 75kb region in the middle. Within weeks, on April 8, 1993, we both discovered the same gene *on the same day*, in the middle of the candidate region. We have been collaborators ever since, and it has been one of the most rewarding relationships of my career.

I learned so much about the power of rare events studying SCA1. As Harry and I delved into mechanisms driving SCA1, we never imagined our genetic studies would reveal how relevant our work would turn out to be for the more common neurodegenerative "proteinopathies" such as Alzheimer's and Parkinson's disease. Our various animal models are allowing us to finally solve the mystery of cell-specific vulnerability in the face of broad expression of the disease-causing gene. Working with my colleague Juan Botas, a *Drosophila* geneticist at Baylor, we have relied on cross-species genetic screens to identify therapeutic entry points for SCA1.

Work on Rett progressed more slowly, proving Art's point about the difficulty of solving a sporadic disease. I had collected DNA samples from over 200 Rett girls—and nearly as many disappointing results. One patient had a translocation on the X chromosome, but there was no gene at the breakpoint. Another had an inversion on the X chromosome but again, no genes to be found at the breakpoints. We collaborated with Carolyn Schannen and Uta Francke and pooled our efforts on three families with two affected females in each to exclude about two-thirds of the X chromosome, but this left us a big region to wade through. I found a family with two second-half cousins with Rett who were related through maternal lines, but the affected girls shared no part of the X chromsome.

After a decade of negative results, research support evaporated: reviewers didn't believe Rett was genetic. Colleagues kept urging me to put my energy into a more common disorder like autism. But I was convinced Rett had to be genetically determined. One person who always encouraged me to keep following my instinct was Victor McKusick. Thankfully, a fellowship from the International Rett Syndrome Association and funding from the Howard Hughes Medical Institute (HHMI) allowed me to keep going. HHMI also allowed me to discover atonal homolog 1, in collaboration with Hugo Bellen, that took me into many interesting areas of biology, including balance, cancer, deafness, and breathing.

At long last, in 1999, my fellow, Ruthie Amir, found the genetic mutation that causes Rett. Igna van den Veyver had observed altered methylation in a Rett patient, which got us thinking about methyl-CpG-binding protein. Since then, understanding how loss of MeCP2 causes Rett syndrome has been a major focus of my lab. Our animal model studies also led us to patients with *MECP2* duplication syndrome, which we showed can be "corrected" in mice when MeCP2 protein levels are returned to normal. Adrian Bird's lab had shown that features of Rett syndrome can also be corrected in mice after restoring the gene. These results tell us that the brain architecture is intact enough to regain function, when we find a treatment. Thanks to advances in sequencing, we now know that Rett is one of the most prevalent causes of syndromic autism, and that like Rett, autism is caused by *de novo* sporadic mutations the majority of the time.

Inspired by the successful collaborations, we founded the Jan and Dan Duncan Neurological Research Institute (NRI) in 2010. Relying on genetics, cross-species studies, and an environment that fosters collaboration, the NRI faculty have discovered the genetic underpinnings of dozens of disorders, and are advancing therapies for several.

My special thanks to:

- My incredible Baylor colleagues and wonderful chair Brendan Lee. The collaborative and nurturing environment of our department has made my career pure joy.
- Beyond mentors and colleagues, the support of family and friends was essential at every step of my career.
- My husband, William, who has been my partner every step of the way while leading his own passionate and successful career in cardiology. His unconditional love and support while we raised our two children, Roula and Anthony, allowed me to go to the lab on nights and weekends and gave me the emotional support I needed when the rewards did not come from experiments.
- My other extended family of trainees, "the Zoghbians," make my career in science a most rewarding one. The 87 graduates and the current 23 trainees have taught me as much as I have taught them. Their hard work, commitment, and passion give me faith that neurogenetics and disease research will be in capable hands for decades to come. Thank you.