Profile

Harry T Orr: decoding spinocerebellar ataxias

Although he has spent most of his career cracking the mysteries of spinocerebellar ataxias, Harry T Orr, a Professor in the department of Laboratory Medicine and Pathology and Director of the Institute for Translational Neuroscience at the University of Minnesota (Minneapolis, MN, USA), never envisioned this path for himself. "I thought I would follow my father into engineering", Orr tells *The Lancet Neurology*. "However, after choosing biology as an extra science at school, I found it fascinating."

Raised in Birmingham, MI, USA, Orr studied marine biology at the University of Miami (FL, USA). He then decided this discipline was too observational for his liking and instead went to Oakland University (Rochester, MI, USA), where he felt lucky to be accepted to work in an eye institute funded by the US National Institutes of Health. Later, he completed a PhD in neurobiology at Washington University (St Louis, MO, USA), mentored by Oliver Lowry (of Lowry protein assay fame), before publishing one of his first papers in 1976, that demonstrated the importance of the cyclic GMP system in retinal photoreceptor dark adaptation. Uncertain about where to direct his postdoctoral studies, Orr decided to spend some time at Harvard University (Cambridge, MA, USA) to learn about recombinant DNA with Jack Strominger, and research the primary structure of human leukocyte antigen (HLA) class I antigens. He then returned to the American midwest in 1981 to extend his work on HLA as an independent faculty member at the University of Minnesota.

One day in 1984, Orr's life would change forever when into his office walked Larry Scott, a neurologist from a family with spinocerebellar ataxia type 1 (SCA1), along with geneticist Elving Anderson. They had just shown that SCA1 was linked to the HLA complex, and wanted Orr to work with them to find the genetic cause. In 1988, Orr learned that Huda Zoghbi (Baylor College of Medicine, Houston, TX, USA) was working on this same mystery. She called him to discuss their mutual goal: "Huda suggested we collaborate, I agreed", says Orr. There would soon be another important call between them. Originally, they thought they were looking for two separate genes, but Zoghbi reanalysed data and called to tell Orr she believed they were searching for the same gene. "Huda proposed we work together to find this gene, and after a long pause I said yes, and have never regretted it. There began three decades of collaboration and friendship." Both researchers identified the gene—called ATXN1—on the same day on April 11, 1993, and excitedly sent each other faxes announcing the discovery.

"When I was new to the field, Harry was already an established leader and influenced my perspective of an ideal scientific career", says J Paul Taylor, Chair of Cell and Molecular Biology at St. Jude Children's Research Hospital in Memphis, TN, USA. "He pursued the logical progression of his own data, untroubled that concepts emerging from his work did not conform to prevailing views at the time. Indeed, as popular scientific opinions have gone in and out of fashion, Harry's discoveries with his colleague Huda Zoghbi, and the hypotheses that evolved from their work together, have been validated with time. He is also very generous with his time and insightful with his advice."

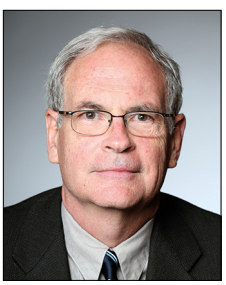
Orr is eternally grateful to the many SCA1 families who have worked with himself and Zogbhi. "All we know about SCA1 is thanks to these families who were prepared to give samples and be studied for all these years", he says. "Far beyond the science, I've attended family events, got to know them all and, sadly, seen many pass away. But like us, all these families are hopeful that we are close to a breakthrough on treatment."

Today, Orr's lab is working to develop SCA1 drug therapies. "The scientific challenge to develop treatments for these kinds of genetic diseases is enormous", he explains. "All our work to date suggests that the earlier we intervene in patients (meaning early childhood), the better the outcome will be. Currently, as with other autosomal dominant conditions, many patients do not want to know if they are affected as there is nothing they can do. This would change rapidly if effective therapies become available." As he is not a clinician, Orr will not be running any future clinical trials, and it will "be hard to have to watch these trials from the side-lines".

However, much work remains to understand the pathophysiology of the disease, and Orr's team is keen to continue. "We want to know how SCA1 affects the brainstem, especially relating to premature mortality", he explains. He is investigating the cholecystokinin gene (*CCK1*) and resultant peptide, which could be part of a protective pathway involving the brain's Purkinje cells, which are affected by many ataxias. "We are in the very earliest stages of this work but, should we confirm this novel function for *CCK1*, we may have a treatment target for all these various ataxias."

Outside of work, Orr enjoys family life with wife, Bonnie, his two daughters, and two grandsons. And to really wind down, he has gone every year for the past 20 years on a white water rafting expedition in Utah and Colorado. "It's grown every year, with scientists, students and their friends tagging along. We are becoming quite well known!" he laughs.

Tony Kirby



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For more on **discovering the mutation in *ATXN1*** see *Nature Genetics* 1993; **4:** 221–26

For the role of **Ataxin-1 in SCA1 mice** see *Cell* 1998; **95:** 41–53

For more on the **pathology of SCA1** see *Neuron* 2018; **97:** 1235–43

For **Purkinje cell involvement in SCA1** see *Cell* 2006; **127:** 697–708