OBITUARY

Raymond Leslie White (1943–2018)

Louis J. Ptáček[1,*]

Raymond Leslie White

Raymond Leslie White was born in Orlando, Florida on October 23rd, 1943, during the second World War. His dad, Larry, was a navigator on B-29s and his mom, Marjorie, was a belle from an old Florida family. After the war, they moved back to his father's hometown of Springfield, OR, where Ray grew up hunting and fishing with his dad and acquired his life-long love of the outdoors and nature. Ray attended college at the University of Oregon. His mentors in the Department of Microbiology, Frank and Mary Stahl, and George Striesinger, thought Ray had great potential as a scientist and supported his application to MIT, where he subsequently attended graduate school and received his Ph.D. under the guidance of Maury Fox.

Ray spent many long days working in the lab, but he also found some time to enjoy skydiving with his friends. Early in his stay in Cambridge, he met his future wife, Joan Distin, who had come to MIT for her first job. They fell in love at first sight and were engaged to be married 3 months later. Together, they spent 5 years in Cambridge, along with many happy weekends in the New England backcountry and in Connecticut, at Joan's family home.

With a tiny inheritance from Joan's grandfather, Joan and Ray bought half ownership of a 2-seater 1946 Luscombe and started flying lessons, mostly with Joan's brother. When it came time for them to move to Stanford University for Ray's post-doctoral work with David Hogness, Ray flew the plane across the country, and Joan would meet him at little airports along the way to camp out for the night. During their 3 years in Palo Alto, Joan and Ray engaged in some new, personal genetic experiments—their two children, with whom they eventually shared many adventurous activities, including flying, sailing, and floating on western rivers.

Ray's post-doc with Hogness focused on genetics in *Drosophila melanogaster.* In 1975, after a very successful 3-year fellowship, Ray moved to the University of Massachusetts School of Medicine to take his first faculty position, which lasted 5 years. It was during this time that Joan began a long and award-winning career as an artist. In 1980, Ray was recruited to the University of Utah in the Department of Cellular, Viral, and Molecular Biology. During this time, his work in genetics continued to evolve toward more complex organisms (i.e., *Homo sapiens*).

Later that year, Ray (along with David Botstein, Ron Davis, and Mark Skolnick) published a seminal *American Journal of Human Genetics* paper that proposed the systematic development of anonymous human genetic markers and their placement into chromosomal maps of the human genome.[1] Part of the attraction of moving to the University of Utah had been the access to a substantial population of large Mormon families. Ray and his colleagues collected DNA samples from more than 1,000 individuals in 3-generation families to use as a mapping panel for the genetic markers he (and others) had begun to identify and develop. For a family to be included, there had to be four living and healthy grandparents, two living and healthy parents, and a sibship of 10 or more children (the so-called "10-sib families"). This was a panel large enough to map markers with (at the time) exquisite precision. The samples and cell lines were housed at the Centre d'Etude du Polymorphisme Humain (CEPH), and were the first example of a distributed resource that enabled broad international collaboration on a biological problem. Ultimately, the CEPH families' samples were used by all of the major groups involved in building human genetic maps so that data generated by different groups could all be placed into the same genomic framework.

In 1984, Ray became chair of the newly formed Department of Human Genetics at the University of Utah. In that same year, at the request of Mortimer Mendelsohn, Ray

[1]Distinguished Professor of Neurology, University of California, San Francisco, San Francisco 94143, USA
*Correspondence: ljp@ucsf.edu
https://doi.org/10.1016/j.ajhg.2018.11.015.

organized a DOE-funded meeting that many now refer to as the "Alta Conference." It was held at the Alta ski resort a short distance from the University of Utah. Always having had an incredible eye for talent, Ray invited an extraordinary group of molecular biologists and human geneticists. Ray had a truly unique power of personality that pushed out the boundaries of this new era in the field of human genetics. A real crucible, this meeting bubbled over with excitement and ideas. Many of the young attendees were destined to become luminaries in their respective fields. From this meeting, many came away with a new vision for how human genetics might develop as a field. Until this point, *Homo sapiens* presented significant problems as a genetic organism. This changed as a result of Ray White's daring and creative vision.

Ray's pioneering work created the foundation for modern human genetics, and this foundation has transformed our understanding of virtually every human disease. He played a seminal role in the technical development of human genetic maps; his role in collecting the CEPH family mapping set that was universally employed for map development was particularly important. Early on, the only available markers were restriction-fragment-length polymorphisms (RFLPs). Ray's group identified a new class of genetic markers that are cleaved by restriction enzymes to produce fragments of many different lengths.[2] This polymorphism is due to variation in the number of tandem repeats (VNTRs) of a DNA sequence. The VNTRs can be detected by Southern blotting. Because most individuals will be heterozygous at such loci, these markers are highly informative for linkage analysis. This discovery set the stage for subsequent identification of short tandem-repeat markers (also called microsatellites), which are also highly polymorphic.

Ray not only developed genomic technology but also applied it to important medical conditions. In some of the earliest DNA-marker studies, Ray and his trainee Web Cavenee, discovered a fundamental mechanism underlying tumor development. They showed that although one copy of the "retinoblastoma gene" can be inherited (in an autosomal-dominant fashion), the other is often lost during tumor development. Ray and Web recognized the deleted allele as "loss-of-heterozygosity" by referencing polymorphic markers.[3] The family inheritance of susceptibility is dominant, but on a cellular level, the disease is recessive. This was the first molecular confirmation of Knudson's tumor suppressor hypothesis and marked the realization that many cancer genes act as tumor suppressors. Both copies of the gene are inactivated in cancer cells. This realization provided the basis for an approach to identifying a wholly new and important class of tumor genes, the "tumor suppressors," which are now known to be critical in tumorigenesis.

As Ray's lab developed thousands of genetic markers, they used the CEPH mapping panel to place them in chromosomal maps of the human genome at ever-increasing density. They then went on to use these reagents to genetically map many important human disease genes. Ray subsequently focused on two genes: neurofibromin 1 (*NF1*, mutations in which cause neurofibromatosis type 1)[4,5] and adenomatous polyposis coli (*APC*, a gene involved in colon cancer).[6] He used positional cloning to identify the causative genes and mutations in these conditions.[7–10] Ray went on to study the *in vitro* functions of the relevant proteins and discovered the function of *NF1* in regulating cell growth, revealing the underlying molecular pathophysiology of this disease through discovery of a key functional domain that had GAP (GTPase activating protein) activity.[11] This discovery meant that the encoded protein (neurofibromin) was most likely responsible for inhibiting the activity of Ras proteins, known to be potent mediators of cellular signaling systems. This subsequently led to the testing of farnesyl inhibitor drugs in mouse models, and the drugs were found to improve the cognitive disorders associated with *NF1* mutations. This offered hope for new therapeutic approaches for treating neurofibromatosis.[12] Ray was therefore a pioneer at every step in the central human genetic paradigm, and his work transformed the field of human genetics in a way that revolutionized biomedical and translational research. His discovery of *NF1* and *APC*, and subsequent molecular characterization of the implicated proteins, provided the foundation upon which all subsequent genetic disease studies now rest.

In 1990, the Human Genome Project was launched. Ray's (and others') genetic markers and maps were used for building physical maps of large insert clones, which were then shot-gun subcloned and sequenced. Thus, Ray's genetic mapping efforts were also foundational to the Human Genome Project.

Ray had a rare capacity to lead in both the lab and the cultural and political arenas of academic leadership. With Ray Gesteland, he was responsible for building the Eccles Institute of Human Genetics at the University of Utah. In addition to housing the Department of Human Genetics, the Institute also housed a new incubator program for Human Molecular Biology and Genetics (the brainchild of Ray, Steve Prescott, and Michael Simmons). In 1994, Ray became the Chairman of the Department of Oncological Sciences at the University of Utah and became the founding Director of the new Huntsman Cancer Institute. In 2002, believing the time was right to embark on the challenging road of complex genetics, he moved to the University of California, San Francisco School of Medicine. There, until his health began to fail, he served as the Director of the Ernest Gallo Clinic and Research Center, the Rudi Schmid Distinguished Professor in neurology, and Vice Chair of the Department of Neurology.

In reading through Ray's bibliography, one notes that he has trained many leaders in their respective fields. Ray also generously supported and mentored many individuals with whom he never shared authorship. During my own time as a fellow in his lab, Ray edited every paper I wrote and, at the end, removed his name from the author list.

He did this despite having made fundamental intellectual contributions, not to mention offering financial support to acquire reagents for all of my experiments. I am just one example of the many trainees and mentees who have benefited from Ray's generous and selfless mentorship. His impact on the field of human genetics has thus been even greater than might be imagined simply from perusing his own publication record.

In recognition of his accomplishments, Ray was elected to the National Academy of Sciences (1992), the American Academy of Arts and Sciences (2005), and the National Academy of Medicine (2005). He received many awards, including the American Society of Human Genetics Allan Award (1989),[13] the General Motors Cancer Research Foundation Charles S. Mott Prize (1990), and the National Health Council's National Medical Research Award (1991), to name a few.

Ray's presence in the field will be greatly missed. He was a giant among men, a maverick always moving toward new horizons and into new areas, where he frequently made monumental contributions. Though gone now, Ray will remain among us, having left a legacy of people whom he trained and mentored and who are now leaders in many areas of biomedical science. His genes will continue to segregate in his wonderful and loving family and, through them and his trainees, he will continue to make our world a better place.

Ray is predeceased by his son Jon Robert White (by a previous marriage) and by his parents, Larry and Margorie White. He is survived by his wife, Joan; his daughter Juliette Palmer White (married to Jon Owen); his son Jeremy Distin White (married to Skylin); his daughter Anne Marie White (by a previous marriage); his grandsons, William Distin Owen and Benjamin Griffin Owen; and his sisters, Susan Mckenzie, Ruth Germaine, and Athalia White.

Acknowledgments

Thanks to Joan Distin White for helpful materials, including the photograph of Ray, and to Neil Risch for helpful comments on the manuscript.

References

1. Botstein, D., White, R.L., Skolnick, M., and Davis, R.W. (1980). Construction of a genetic linkage map in man using restriction fragment length polymorphisms. Am. J. Hum. Genet. *32*, 314–331.
2. Nakamura, Y., Leppert, M., O'Connell, P., Wolff, R., Holm, T., Culver, M., Martin, C., Fujimoto, E., Hoff, M., Kumlin, E., et al. (1987). Variable number of tandem repeat (VNTR) markers for human gene mapping. Science *235*, 1616–1622.
3. Cavenee, W.K., Dryja, T.P., Phillips, R.A., Benedict, W.F., Godbout, R., Gallie, B.L., Murphree, A.L., Strong, L.C., and White, R.L. (1983). Expression of recessive alleles by chromosomal mechanisms in retinoblastoma. Nature *305*, 779–784.
4. Barker, D., Wright, E., Nguyen, K., Cannon, L., Fain, P., Goldgar, D., Bishop, D.T., Carey, J., Baty, B., Kivlin, J., et al. (1987). Gene for von Recklinghausen neurofibromatosis is in the pericentromeric region of chromosome 17. Science *236*, 1100–1102.
5. White, R., Nakamura, Y., O'Connell, P., Leppert, M., Lalouel, J.-M., Barker, D., Goldgar, D., Skolnick, M., Carey, J., Wallis, C.E., et al. (1987). Tightly linked markers for the neurofibromatosis type 1 gene. Genomics *1*, 364–367.
6. Nakamura, Y., Lathrop, M., Leppert, M., Dobbs, M., Wasmuth, J., Wolff, E., Carlson, M., Fujimoto, E., Krapcho, K., Sears, T., et al. (1988). Localization of the genetic defect in familial adenomatous polyposis within a small region of chromosome 5. Am. J. Hum. Genet. *43*, 638–644.
7. Viskochil, D., Buchberg, A.M., Xu, G., Cawthon, R.M., Stevens, J., Wolff, R.K., Culver, M., Carey, J.C., Copeland, N.G., Jenkins, N.A., et al. (1990). Deletions and a translocation interrupt a cloned gene at the neurofibromatosis type 1 locus. Cell *62*, 187–192.
8. Cawthon, R.M., Weiss, R., Xu, G.F., Viskochil, D., Culver, M., Stevens, J., Robertson, M., Dunn, D., Gesteland, R., O'Connell, P., and White, R. (1990). A major segment of the neurofibromatosis type 1 gene: cDNA sequence, genomic structure, and point mutations. Cell *62*, 193–201.
9. Joslyn, G., Carlson, M., Thliveris, A., Albertsen, H., Gelbert, L., Samowitz, W., Groden, J., Stevens, J., Spirio, L., Robertson, M., et al. (1991). Identification of deletion mutations and three new genes at the familial polyposis locus. Cell *66*, 601–613.
10. Groden, J., Thliveris, A., Samowitz, W., Carlson, M., Gelbert, L., Albertsen, H., Joslyn, G., Stevens, J., Spirio, L., Robertson, M., et al. (1991). Identification and characterization of the familial adenomatous polyposis coli gene. Cell *66*, 589–600.
11. Xu, G.F., O'Connell, P., Viskochil, D., Cawthon, R., Robertson, M., Culver, M., Dunn, D., Stevens, J., Gesteland, R., White, R., and Weiss, R. (1990). The neurofibromatosis type 1 gene encodes a protein related to GAP. Cell *62*, 599–608.
12. Kim, H.A., Ling, B., and Ratner, N. (1997). Nf1-deficient mouse Schwann cells are angiogenic and invasive and can be induced to hyperproliferate: Reversion of some phenotypes by an inhibitor of farnesyl protein transferase. Mol. Cell. Biol. *17*, 862–872.
13. White, R. (1990). 1989 Allen Award address: The American Society of Human Genetics annual meeting, Baltimore. Am. J. Hum. Genet. *47*, 892–895.