

Haig H. Kazazian, Jr. (1937–2022)



Norman Arnheim (left) and Haig Kazazian (right) in December 1988 at the Banbury Meeting, "Polymerase Chain Reaction." (Image courtesy of Cold Spring Harbor Laboratory Archives.)

Dr. Haig H. Kazazian, Jr. passed away on January 20, 2022 in Baltimore, Maryland. He was a towering figure in human molecular genetics, and his research contributions and academic mentorship transformed our understanding of the causative role of the genetic variation in phenotypic variation.

Haig was born in 1937 to Armenian immigrants and was raised in Toledo, Ohio. His mother immigrated to the USA from Constantinople (now Istanbul) in 1920. His father, hailing from the Ottoman city Kayseri, survived a forced march from Anatolia to Aleppo, Syria, and life in a concentration camp during World War I. In 1917 his father escaped, via Damascus and Cuba, to Toledo, Ohio, where he joined his uncle in the Oriental rug business.

Haig received his B.A. degree from Dartmouth College in Hanover, New Hampshire in 1959. He then continued as a medical student there for two years and completed an M.D. degree at Johns Hopkins School of Medicine in Baltimore in 1963. During his last year in medical school he met Barton Childs, who introduced him to human genetics and became his lifelong mentor. After two years of pediatrics training at the University of Minnesota Hospital in Minneapolis, Haig returned to Hopkins. In his first research experience, Haig worked on X-Chromosome dosage in the laboratory of Bill Young, a *Drosophila* geneticist. Then, as many other academically inclined physicians during the Vietnam war era, he entered the Public Health Service at the National Institutes of Health (NIH) as an alternative to military service. He joined the laboratory of Harvey Itano, where he began studies of hemoglobin synthesis at the dawn of the molecular biology revolution. Following this intensive, postdoctoral experience, Haig returned to Hopkins in 1969 as a faculty member in pediatrics. He received his first NIH grant the year after, beginning 50+ years of continuous NIH funding. As early as

1977 he had established a molecular prenatal diagnostic service at Hopkins following the pioneering carrier screening of Tay-Sachs disease in the Baltimore-Washington Jewish community by Michael Kaback. However, his seminal contributions focused on the molecular basis of beta thalassemia and the role of retrotransposons (i.e., "jumping genes") in human biology.

The careers of both authors of this piece were immeasurably enhanced through their close association with Haig—S.E.A. as a post-doctoral fellow and subsequently a scientific collaborator, and S.H.O. as a scientific collaborator at the time he established his own laboratory at Boston Children's Hospital. A landmark contribution of Haig's laboratory was the discovery of haplotypes of common polymorphic sites around the beta globin genes (Antonarakis et al. 1982). This work followed soon after the discovery of an association of a single polymorphic site in the beta globin locus with the sickle cell mutation, and suggested a surprisingly simple way to identify the numerous, independent pathogenic variants leading to beta thalassemia. The molecular tools at the time were primitive compared to those available today. PCR had not yet been invented. Genomic cloning was new and still considered an "art." One of us (S.H.O.) had begun cloning beta globin genes from DNA samples of thalassemia patients but had no way to avoid repeatedly isolating the same mutation again and again, if it were frequent in a population. Parsing patient samples on the basis of their beta globin haplotypes provided a highly efficient strategy to identify the diversity of mutations in beta thalassemia. Over the course of several years (1980–1984), the collaboration of Haig and S.E.A. with S.H.O. led to the first comprehensive molecular description of a human disease (Orkin et al. 1982). Beyond this application of the haplotype concept, Haig's collaboration with Aravinda Chakravarti established the principle of linkage disequilibrium blocks and recombination hotspots (Chakravarti et al. 1984), both instrumental for the subsequent establishment of the HapMap Project (The International HapMap Consortium 2005).

Early on, the beta globin gene occupied a special place in the field of human genetics and genomics since many of the lessons learned regarding the diversity of pathogenic variants stem from the hemoglobinopathies. The Kazazian laboratory became an international center for mutation searches of Mendelian phenotypes. With this success came Haig's appointment as Director of the Pediatric Genetics division and later the Director of the Center of Medical Genetics at Hopkins. Haig created a rich training environment, which attracted outstanding trainees and young faculty (Antonarakis 2020). Gregg Semenza, who received the Nobel Prize in Physiology and Medicine in 2019, began his work on oxygen signaling in this environment (Semenza et al. 1991; Semenza and Wang 1992).

In the mid-1980's Haig and S.E.A. decided to work on the relatively common X-linked bleeding disorder hemophilia A, in order to identify, in an unbiased way, the full spectrum of human pathogenic variants. The rationale was that males with one X Chromosome would show the phenotypic effects of all deleterious mutations in the coagulation factor VIII (*F8*) gene that cause

Corresponding authors: stylianos.antonarakis@unige.ch, Stuart_Orkin@dfci.harvard.edu

Article published online before print. Article and publication date are at <https://www.genome.org/cgi/doi/10.1101/gr.276712.122>. Freely available online through the *Genome Research* Open Access option.

© 2022 Antonarakis and Orkin This article, published in *Genome Research*, is available under a Creative Commons License (Attribution-NonCommercial 4.0 International), as described at <http://creativecommons.org/licenses/by-nc/4.0/>.

hemophilia A. One notable first discovery was the hypermutability of CG dinucleotides (Yousoufian et al. 1986). However, the observation that changed the direction of Haig's subsequent research was the identification of an insertion of a LINE transposable element within the *F8* gene sequence causing hemophilia A (Kazazian et al. 1988). This exciting discovery had a critical impact on Haig. He wrote in his autobiographical paper, "it took me about five seconds to decide that I will focus the entire lab on jumping genes" (Kazazian 2021). The "jumping genes" journey was a happy ride of important discoveries and excitement (Kazazian and Moran 2017). Haig's lab isolated an active transposable element and worked out the molecular events of retrotransposition. They devised with John Moran a laboratory assay for retrotransposition (Moran et al. 1996), worked out nonautonomous retrotransposition, and discovered somatic retrotranspositions and somatic LINE-1 insertions in cancer. The Kazazian laboratory was the world's center of retrotransposition in the human genome. In 1994, in the middle of the jumping gene stories, Haig moved to the University of Pennsylvania as Chairman of the Department of Genetics. He established there an outstanding department of younger investigators who were successful contributors to the growing field of human genetics under his guidance and mentorship. In 2010 he returned to Hopkins as a professor in the McKusick-Nathans Institute of Genetic Medicine, which has recently become a department. In 2020 he decided to leave laboratory research after more than 50 years of work. He remained a reference point and a treasure trove of wisdom in the department for both young and old faculty members. As he said, "it's been a great run, and I've loved every minute of it" (Kazazian 2021).

In 2011, Haig wrote in his autobiographical book, "Mobile DNA: Finding treasure in junk," regarding a career in scientific research: "You've got to burn to do research, you can't go at it with half-hearted enthusiasm or self-doubt" (Kazazian 2011). Then he goes on and gives some advice regarding the training years: "You want someone who will discuss your research with you on a daily basis, perhaps so much so that you feel that he or she is pestering you all the time for new data ... Your trainers also need to be available for discussion of all kinds of problems, both those that you face in the lab and those that are related to other aspects of your life." Regarding a mentor in the first five to 10 years as a faculty member, he says: "Having an interested, accessible, and experienced mentor is crucial to success in science. Behind every good scientist is an outstanding mentor." He also felt the responsibility to be a good mentor himself and he thoroughly enjoyed this part of the academic career, even when the mentee was at another university (e.g., Aravinda Chakravarti). He was a fervent advocate of openness in presenting and discussing new data. He advises, "it is best to discuss your science with a wide range of all scientists, including those within your immediate field, those in the broader field, and those in other fields of biomedical science. You never know from where the next good experimental idea will come." And some wisdom on collaborations: "Collaborations with other scientists should be welcomed as a way to broaden one's scientific outlook and scope."

Haig was fascinated with and excited by new scientific data. He literally jumped every time he heard something innovative, and his enthusiasm was contagious. He was a self-effacing mentor, an outstanding collaborator, a straight shooter without a hidden agenda, and a valuable colleague. His preferred workplace was in the middle of his lab, constantly talking to and inspiring people (Antonarakis 2009).

In 2008, Haig's work was acknowledged with the William Allan Award, the top honor of the American Society of Human

Genetics, and the most prestigious recognition in human genetics (Kazazian 2009). He was elected to the National Institute of Medicine and the National Academy of Sciences. The "globin" crowd was honored by several other Allan Awards (Yuet Wai Kan 1984, Antonio Cao and Michael Kaback 1993, David Weatherall 2003, Aravinda Chakravarti 2013, Stuart H. Orkin 2014, Stylianos E. Antonarakis 2019) and Haig had an influence in the achievements of the majority of these scientists.

Haig was enormously proud of his Armenian heritage. At the reception after Gregg Semenza's 2019 Nobel talk in Stockholm, Haig was delighted to meet an Armenian professor. They had a lengthy discussion on Armenian food, customs, and jokes and seemed as if they both found this much more interesting than socializing with the exclusive crowd of Nobel guests and laureates.

Haig was an exemplary family man. He met his wife Lilli, a nursing instructor, at breakfast in the medical dormitory cafeteria at Hopkins in 1961, and they were married the year after. Haig is also survived by two children, Haig and Sonya, and five grandchildren. Haig described Lilli as his best friend and the love of his life, and their marriage spanned 60 wonderful years (Kazazian 2021).

Haig will be sorely missed, but fondly remembered!

Stylianos E. Antonarakis

Department of Genetic Medicine and Development, University of Geneva Medical School, Geneva, Switzerland

Stuart H. Orkin

Harvard Medical School and Howard Hughes Medical Institute, Boston, Massachusetts, USA

References

- Antonarakis SE. 2009. William Allan Award introduction: Haig H. Kazazian, Jr. *Am J Hum Genet* **84**: 103–104. doi:10.1016/j.ajhg.2009.01.002
- Antonarakis SE. 2020. 2019 William Allan Award. *Am J Hum Genet* **106**: 289–294. doi:10.1016/j.ajhg.2020.02.005
- Antonarakis SE, Boehm CD, Giardina PJ, Kazazian HH Jr. 1982. Nonrandom association of polymorphic restriction sites in the β -globin gene cluster. *Proc Natl Acad Sci* **79**: 137–141. doi:10.1073/pnas.79.1.137
- Chakravarti A, Buetow KH, Antonarakis SE, Waber PG, Boehm CD, Kazazian HH Jr. 1984. Nonuniform recombination within the human β -globin gene cluster. *Am J Hum Genet* **36**: 1239–1258.
- The International HapMap Consortium. 2005. A haplotype map of the human genome. *Nature* **437**: 1299–1320. doi:10.1038/nature04226
- Kazazian HH Jr. 2009. Allan Award Lecture: on jumping fields and "jumping genes". *Am J Hum Genet* **84**: 105–114. doi:10.1016/j.ajhg.2009.01.003
- Kazazian HH Jr. 2011. *Mobile DNA: finding treasure in junk*. FT Press, Upper Saddle River, NJ.
- Kazazian HH Jr. 2021. A long, fulfilling career in human genetics. *Annu Rev Genomics Hum Genet* **22**: 27–53. doi:10.1146/annurev-genom-111620-095614
- Kazazian HH Jr., Moran JV. 2017. Mobile DNA in health and disease. *N Engl J Med* **377**: 361–370. doi:10.1056/NEJMr1510092
- Kazazian HH Jr., Wong C, Yousoufian H, Scott AF, Phillips DG, Antonarakis SE. 1988. Haemophilia A resulting from *de novo* insertion of L1 sequences represents a novel mechanism for mutation in man. *Nature* **332**: 164–166. doi:10.1038/332164a0
- Moran JV, Holmes SE, Naas TP, DeBerardinis RJ, Boeke JD, Kazazian HH Jr. 1996. High frequency retrotransposition in cultured mammalian cells. *Cell* **87**: 917–927. doi:10.1016/S0092-8674(00)81998-4
- Orkin SH, Kazazian HH Jr., Antonarakis SE, Goff SC, Boehm CD, Sexton JP, Waber PG, Giardina PJV. 1982. Linkage of β -thalassaemia mutations and β -globin gene polymorphisms with DNA polymorphisms in human β -globin gene cluster. *Nature* **296**: 627–631. doi:10.1038/296627a0
- Semenza GL, Wang GL. 1992. A nuclear factor induced by hypoxia via *de novo* protein synthesis binds to the human erythropoietin gene enhancer at a site required for transcriptional activation. *Mol Cell Biol* **12**: 5447–5454. doi:10.1128/mcb.12.12.5447-5454.1992
- Semenza GL, Neifelt MK, Chi SM, Antonarakis SE. 1991. Hypoxia-inducible nuclear factors bind to an enhancer element located 3' to the human erythropoietin gene. *Proc Natl Acad Sci* **88**: 5680–5684. doi:10.1073/pnas.88.13.5680
- Yousoufian H, Kazazian HH Jr., Phillips DG, Aronis S, Tsiftis G, Brown VA, Antonarakis SE. 1986. Recurrent mutations in haemophilia A give evidence for CpG mutation hotspots. *Nature* **324**: 380–382. doi:10.1038/324380a0