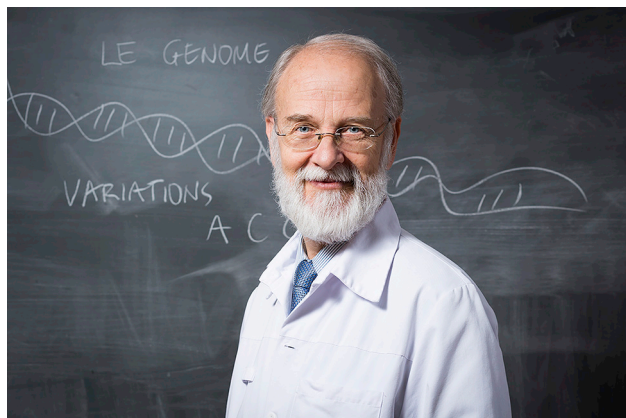


2019 William Allan Award¹Stylianos E. Antonarakis^{2,*}

Thank you, Haig for your kind and generous words! It is an immense honor for me to receive this award!

To borrow from Shakespeare's pen (*Twelfth Night*, Act III, Scene 3), "I can no other answers make but thanks and thanks"!

Acceptance speeches have the tendency to become emotional, stereotyped, and self-promoting... I am afraid that I may lack originality here and fall into some of these clichés.

Awards have two components: the givers and the receiver. Without a giver there is no receiver. I wish to thank the chair, Dr. Fowzan S. Alkuraya, and all the members of the awards committee for this great gift to me and the members of both our research laboratory and clinical genetics services.

When I looked at the distinguished list of the previous awardees since 1962 (see [Web Resources](#)), I experienced vertigo: all of these past awardees, these extraordinary women and men that have made tremendous contributions to human genetics/genomics, were my heroes and role models! I am delighted and honored to be in their exclusive company.

If I put a label on our research, I would classify myself as someone who is obsessed by, and works, on high-impact variants, i.e., genomic alterations that have a significant impact on the phenotype. And contrary to what some of my colleagues may think, I argue that we have not yet finished with the high-impact variants. We are not even in the middle of the road; only 4,450 from the 20,000 pro-

tein-coding genes have been linked to a Mendelian phenotypic variability to date. There is a long way to go and much to be learnt from the (near) Mendelian genes.

With an MD degree from the University of Athens, a couple of years of clinical residency, lots of dreams, and the memory of the splendid view of the Acropolis when I opened my window back home, I arrived in Baltimore on a humid and 100°F hot summer day. I put my suitcase in the then-miserable Reed Hall across from the Hopkins dome and went directly to the lab on CMSC10. I found Haig Kazazian sitting in the middle of the lab talking to people around him as they were pipetting or loading a gel or looking at bands on a film. He was a warm, unpretentious, civilized, curious, talkative gentleman, with a burning internal fire for conquering the unknown. Fifteen minutes of conversation (even with my terrible English accent), and the fact that he was there in the middle of the lab, convinced me that this was what I was looking for; in my mind, this environment was comparable to that of the Morgan lab at Columbia that I had read about extensively. In the next 13 years, Haig walked me through the wonders of lab work, helped me to dream of restriction sites, and showed me the way to become an independent investigator, a fair competitor, a collaborator, and a friend.

As a child I had played so much in the surroundings of Acropolis! In addition, my brain was bombarded with the classic education at school and the thinking of the people that lived around my playground more than 110 generations ago. One short phrase that stuck in my mind for years was "Know thyself" that was inscribed in the Temple of Delphi. In an essay I wrote in middle school on this topic, unlike the rest of the class, I wrote "know thyself" for me means to know your muscles, and liver, and nerves and lungs and kidneys; these are the elements that make yourself! The teacher was not that happy with this... she was correctly thinking like Socrates in the discussion with Euthydemus (as described in Xenophon's *Memorabilia*).

Strangely, during medical school, I loved anatomy and Andreas Vesalius: structure informs function. I was also intrigued by the individualism of blood transfusions and non-compatibility of different people. Hippocrates came to my rescue: he wrote "Idiosyncrasy predisposes to or protects from certain diseases: The therapeutic strategy depends on the idiosyncratic differences."¹

¹This article is based on the address given by the author at the meeting of the American Society of Human Genetics (ASHG) on October 15, 2019, in Houston, TX, USA. The video of the original address can be found at the ASHG website

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Figure 1. The Johns Hopkins Genetics group circa 1990. Shown from left to right: 1st row: Emily Pasterfield, Victor A. McKusick, Haig H. Kazazian, Reed E. Pyeritz, David Valle. 2nd row: Barbara R. Migeon, Beth A. Dombroski, Ethylin (Mimi) W. Jabs, Sue Penno, Bill Kerns, Corinne D. Boehm, Melvin G. McInnis, George H. Sack, Stylianos E. Antonarakis. 3rd row: Gail Stetten, Allan F. Scott, Garry R. Cutting, Karen J. Hofman, Lilly Kazazian, E. Anthony (Tony) Murphy, Gloria Petersen, Karin Blakemore, Gregg L. Semenza. 4th row: Jill Hennessy, Clair Francomano, Orest Hurko, Philip Hieter, Ada Hamosh, John D. Gearhart, Neil A. Holtzman, George Thomas, Michael Geraghty. 5th row: Connie Griffith, Barbra Schmeckpepper, Terry Bishop, Forrest Spencer, Kathryn McGowan, Linda Cooper, Cathy Lawson, Virginia L. Corson, Wilma B. Bias. 6th row: Andrew C. Warren, Hugo Moser.

My medical school years were marked with the Greek Dictatorship of the Colonels, a very dark era of the modern European history. I graduated from the University of Athens Medical School in 1975. The generation of my parents Emmanuel and Alexandra had lived in difficult times. My father saw a catastrophic war in the early 1920s in the east side of the Aegean. 1,500,000 refugees came to mainland Greece including my father's side of the family. Subsequently, the parents lived through a German occupation in the early 1940s and a civil war in the late 1940s.

In medical school I was impressed with the study of heredity, particularly the similarities of twins and the pedigrees of β -thalassemia, a hereditary anemia that is quite common in Mediterranean countries. I wish to thank my late professors Phaedon Phessas and Nikos Matsaniotis of the Athens Medical School; each of them introduced me in a different way to the thalassemia world. At that time, George Stamatoyannopoulos also greatly impressed me with his pioneer work. In the late 1960s, fresh out of medical school, he went to Orchomenos, a village in Greece of ~5,000 inhabitants mentioned by Homer in *The Iliad*, to screen, by hemoglobin electrophoresis, the population for sickle cell anemia carriers to provide counselling for this recessive disorder.

Approximately two-thirds of the marriages in Orchomenos were arranged among families. Remarkably, ~23% of the population were heterozygous carriers of the sickle cell trait, and around 1 in 100 neonates was born with

the disease. George examined, screened, and counselled 2,300 individuals over the course of 40 months. This first recorded carrier screening program provided the necessary proof of principle for subsequent screening initiatives, including population-specific programs such as those for β -thalassemia in Mediterranean regions or for Tay-Sachs disease in the Ashkenazi Jewish population.^{2,3}

Heleni, a 20-year-old patient with β -thalassemia, who was also my neighbor, said to me one evening on the balcony of St Sophia Hospital in Athens: why me? Please find out why I am sick, find out a treatment for this disease. She died a few weeks later, and her memory was my constant inspiration throughout my long genetics journey. The 1978 seminal paper of Yuet Wai Kan (1984 Allan Award winner) on the polymorphism linked to the sickle mutation in the *HBB* gene⁴ triggered me to pack my suitcase for Baltimore!

At Hopkins I was lucky to become a member of an important professional pedigree: the Haig Kazazian lineage on one side (that includes the twice Nobel Laureate Linus Pauling and Harvey Itano) and the Victor McKusick (1977 Allan Award winner) lineage on the other. To this date, I probably cannot completely measure the impact of the exceptional privilege to be within such a distinguished pedigree. The Hopkins years were a happy merry-go-round carousel of excitement! We had described polymorphic haplotypes around the beta globin gene,^{5,6} identified many pathogenic variants using the haplotype identity of the mutant alleles (see for example Antonarakis et al.,⁷ Orkin et al.^{8,9}), defined recombination hotspots¹⁰ that provided the proof of principle for the later developed Hapmap project, and contributed to the elucidation of the molecular causes of Hemophilia A.^{11,12} The collaborations with the Stuart Orkin (2014 Allan Award winner) and Aravinda Chakravarti (2013 Allan Award winner) labs on these topics were delightful; it seemed to me that the joy of sharing was greater than the joy of publishing.

The genetics environment at Hopkins in the 1980s was phenomenal. Really phenomenal. I wish to thank everybody in this photo (see Figure 1). The tremendous progress that has taken place in genetics over the last 40 years greatly depended on the contributions of Johns Hopkins Genetics. Thank you Victor McKusick, Barton Childs (1973 Allan Award winner), David Valle, Barbara Migeon, Tony Murphy, Gregg Semenza (2019 Nobel Prize winner), Garry Cutting, Hal Dietz, George Thomas, Kirby Smith, George Dover, Bill Zinkham, Hugo Moser, Clair Francomano, John Phillips, Ned Boyer, John Littlefield, Sam Charache, Harry Ostrer, Robbie Burk, Bert Vogelstein, Gail Stetten, Niel Holzman, Reed Pyeritz, George Sack, Ann Pulver, Mimi Jabs, Allan Scott, Peter Kwiterowicz, Ada Hamosh, Phil Hieter, and all!

We had established one of the first DNA diagnostic labs and learnt almost all the basic lessons for monogenic disorders. I started a project on trisomy 21 (another disease resulting from a high-impact copy-number variation) and

became heavily involved in the genomic analysis of chromosome 21.^{13–17} To touch on complex disorders, we have worked on schizophrenia,¹⁸ not very successfully because the time was premature. Notably, however, we had with colleagues from Harvard identified the link between the VCFS deletion syndrome and strong susceptibility to schizophrenia.¹⁹

My generation is proud of two major contributions: the deciphering of the human genome and the triumph over the mendelian disorders. I was very lucky to be involved in both. Some examples of the thrill of discoveries include those in hemophilia A,^{11,12} the 12-nucleotide expansion in the CSTB gene in progressive myoclonus epilepsy,²⁰ the insertion of satellite repeats in one form of hereditary deafness,²¹ the discovery of the original Kartagener syndrome gene,²² and the identification of the AIRE gene responsible for an autoimmune syndrome among others.²³ The discovery of the gene responsible for a mendelian disorder is a bridge from agnosia to gnosis and development of accurate diagnostic tests, and certainly to therapies.

The Baltimore years ended in 1992. We packed the memories, and the notebooks, deracinated the four children—Emmanuel, Gregory, Alexander, and Christina—kept the friends into special and locked synaptic bonds, and flew the Atlantic the other way back to the old world and the good coffee. Destination Geneva, Switzerland! A small, exclusive, international, science-hungry place where people speak, gossip, and joke in French without being French. I was recruited by Bernard Mach and arrived in my new professorial office on a Monday morning, with pouring rain. The old secretary of the department sized me up and after realizing that my French was not richer than 10 words, she told me the story of the department of genetics: “with the first director, Prof. David Klein, I could have been his daughter; with the second director, Prof. Eric Engel, I could have been his wife; with you, I could be your mother!” She also gave me Darwinian advice: in order to be successful here, scientific excellence is not enough, you must adapt to the environment!

Well! I took her advice to heart and transformed myself for a second time. From Mediterranean to American to central European. I also became very familiar with the Swiss National Science Foundation that I thank tremendously for supporting our research. I was lucky that outstanding people joined our laboratory and genetics clinic and paid attention to the sensitivities of the central European intelligentsia and the expectations of the fellow citizens. A well-known professor called me a few days after my arrival and kindly invited me to speak in a conference. He gave me the title: The Genetics of the X Chromosome. I naturally said: I am delighted, but I do not work on the X chromosome. A silence emerged from the other end, and after a cough he said: “I thought you were a geneticist!”

During the Geneva years, I had the great privilege to work with outstanding colleagues in order to build genetic medicine. We continued to grow genetics in the University and the hospitals, created an interdisciplinary institute of

genetics and genomics (iGE3), and focused on Mendelian genetics, genome function and variation, trisomy 21, and the progressive introduction of genetics in all medical disciplines (see for example Dermitzakis et al.,^{24–26} Reymond et al.,²⁷ Prandini et al.,²⁸ Dimas et al.,²⁹ ENCODE,³⁰ Nikolaev et al.,^{31,32} Djebali et al.,³³ Lappalainen et al.,³⁴ Letourneau et al.,³⁵ Borel et al.,³⁶ Bonilla et al.,³⁷ Santoni et al.,³⁸ Garieri et al.,³⁹ Liu et al.,⁴⁰ Makrythanasis et al.,⁴¹ Popadin et al.,⁴² Delaneau et al.⁴³). I am proud that with other enthusiastic colleagues and the help from the institutions we have created one of the first genome clinics in Europe with the objective of providing diagnostics via high-throughput sequencing of exomes or genomes.⁴⁴ Numerous people have generously helped our laboratory in Geneva to thrive: Jean-Dominique Vassalli, Bernard Fulpius, Pierre Vassalli, Denis Hochstrasser, Guy-Olivier Second, Denis Duboule, Philip Halban, Robin Offord, Peter Suter, Pierre Spierer, André Hürst, Didier Trono, Jacqui Beckmann, and Yves Fluckiger among many others.

I am particularly proud of the successful Genome exhibition in the center of Geneva (in the Ile Rousseau for those of you who have visited the beautiful city), and the introduction of World Down Syndrome Day on March 21st, first organized in Geneva in 2006 and adopted by the UN as an official day in 2012. It is very satisfactory each year to see that the agenda of the meeting is gradually advancing toward a better life for those with Down syndrome and their families.

I have had the privilege of participating in the McKusick Bar Harbor course for the last 40 years! At the most recent Bar Harbor course, Bob Nussbaum said to me that in this acceptance speech he wanted to hear what excites me now: I am thrilled with the consanguinity project in Pakistan, with the contribution of Dr. Muhammad Ansar to discover novel recessive genes associated with mendelian phenotypes such as intellectual disability and visual impairment. Within the initial pilot phase, we have identified 45 new candidate genes in approximately 400 families studied.^{45–51} The other exciting projects are exploring the mechanism of gene dosage imbalance⁵² in trisomy 21 and the chromatin structural changes due to the extra chromosome 21 in the trisomy nucleus.

I thank all my collaborators over the years. I looked at the facts, and I have 10,400 co-authors in our publications. What a pleasure to work with so many dedicated people!

I wish to thank all my dearest outstanding colleagues and friends for the fantastic journey together, the support and criticisms, the excitement of discoveries, the shaping up of our research agenda and priorities, the ideas and debates, and the constructive competition for the benefit of the individuals with genetic disorders and their families.

Very special thanks goes to the patients and their families.

Very special thanks also to my supportive family, Grigoria, Emmanuel, Liz, Gregory, Alexander, Chaido, Christina, Stylianos, Ann-Grigoria, Sophia, Gabriel, Elisabeth, Stylianos, and Athina.

To conclude, I will cite again these inhabitants of today's Greece that lived 110 generations ago: During the public celebrations of Spartans at the time, the younger generation used to say loudly in chorus to the older generation: "...Ἄμες δὲ γ' ἐσόμεθα πολλῶ κάρρονες..." "We will become much better than you!"

I wish to thank all of these outstanding people who joined my laboratory and the clinics over the years, first at Hopkins and then at the University of Geneva. I felt like YOUR student, and I have been delighted to see your scientific development and intellectual achievements.

Among all of them, let me here first wholeheartedly congratulate the 2019 Nobel Laureate, Gregg Semenza, with whom we have studied the *EPO* gene and its regulation by the hypoxia inducible factor.⁵³

I wish also to thank Garry Cutting, Matt McGinniss, Marguerite Neerman, Sergey Nikolaev, Christelle Borel, Siv Fokstuen, Robert Lyle, Samuel Deutsch, Lucia Bartoloni, Maria Lalioti, Uppala Radhakrishna, Michael Petersen, Efi Economou, Roman Chrast, Marie Waterhofer, Hamish Scott, Andy Sharp, Olivier Menzel, Dimitris Avramopoulos, Logos Curtis, Hiroshi Inaba, Caroline Tapparel, Mark Friedli, Periklis Makrythanasis, Emmanuelle Ranza, Catia Attanasio, Ariane Giacobino, Ambroise Wonkham, Michel Guipponi, Haiming Chen, Bernard Conrad, Stephan Eliez, Giuseppe Merla, Kostya Popadin, Pierre Hutter, Isabel Filges, Andreas Massouras, Audrey Letourneau, Jean-Louis Blouin, Federico Santoni, Alexandre Reymond, and Emmanouil Dermitzakis who have now professorial and group leading positions in academia, the clinical sector, and industry! It is a tremendous pleasure to watch their achievements and contributions. I am particularly proud that Alexandre Reymond and Emmanouil Dermitzakis now have leadership positions in Genetic Medicine in the Lausanne-Geneva area of Switzerland. This is certainly a partial list of all the colleagues that have substantially contributed to the research projects and the clinical activities. Furthermore, I wish to thank all the laboratory assistants and the administrative colleagues for their expert support over the years.

Our work is not finished. We have not reached perfection yet, either in terms of understanding the mendelian disorders, or providing treatment for them. When I was a schoolboy I had the great chance of meeting the "Divina," soprano Maria Callas who immensely impressed me with her personality and later on with her perfectionism in her voice. I hope that genetic medicine will soon reach the perfection that she achieved with her superb voice!

And as Shakespeare said in *The Tempest* (Act II, Scene 1): "What is past is a Prologue!"

Thank you again for this exceptional distinction!

Web Resources

Prior Allan Award recipients, <https://www.ashg.org/membership/awards/past-recipients/#william-allan>

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