2017 William Allan Award[1]

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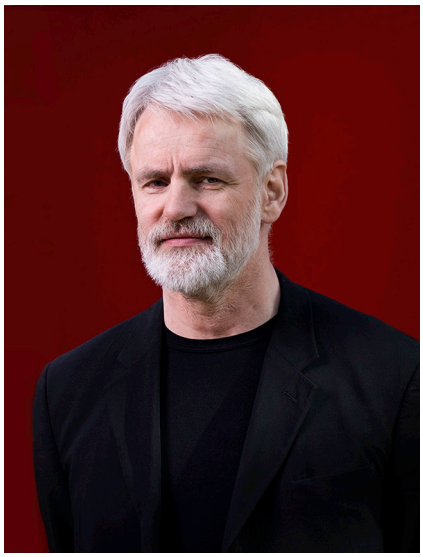

Thank you, thank you for giving me this award. My understanding is that it is given for having contributed to human genetics over a long period of time. My assumption is that I am given this award for what is considered to be a good story that can be told with my work in human genetics. And please do not correct me if I am wrong.

I grew up in a family where storytelling was considered the supreme art form. My father insisted that the only thing that mattered in the end is the story that you could tell with your work, with your life, with your day, with every single moment in your life. It was never clear to me what he was trying to tell us with this, nor was I convinced that he meant this until one day in the late 1980s:

My father broke his right leg at the ankle when he was 20 years of age, and it didn't heal properly. He was sent to the National Hospital of Iceland, where they biopsied the fracture site and told him subsequently that he had osteosarcoma. They amputated his leg at the mid-thigh and told him that he would be dead within 6 months. Decades later, he woke up one day and realized that he had completely failed to die in a timely manner and began to wonder. He asked me to review the slides from the old biopsy, which I did, and to my dismay I found no neoplasm but rather a scar and somewhat distorted tissue. He had been hopping on one leg for decades because of a medical mistake—a misdiagnosis—and the big question was, should I or should I not tell him? I consulted with family and friends, and everybody concluded that I would have to tell him. I sat down with him to bring him the news, and I expected that he would be devastated. But when I told him, his face lit up, and he jumped to his feet (or foot) as swiftly as a one-legged man can and said, " I have to write a book about this," which he did.

In defense of the medical doctors who misdiagnosed my father in 1940, he almost certainly had a mutation in one of the collagen genes that I inherited (this mutation is responsible for the fact that the appearance of my left foot is more befitting of a duck than a human being). And therefore, my left foot has become a part of the history of my father's right leg, which he lost as a young man long before I was born. That's how human genetics works. We human geneticists are historians of human lives—of humanity.

Let's now turn our attention to the history of deCODE Genetics.

When I was 16 years of age, I worked for 3 days during Easter break—hauling liquid concrete in a wheelbarrow—on the construction of a retention wall at a fish farm just outside of Reykjavík. The wheelbarrow was big, the liquid concrete was heavy, and the 12 hr workdays were almost too much for the skinny teenager. It rained cats and dogs during every minute of all 3 days, which made the job considerably more difficult because the wheels of the wheelbarrow sank into the wet ground, and when that happens, a wheelbarrow has a tendency to topple. At high noon on the last day, I lost control of my wheelbarrow, and it toppled. My 2-year-older brother, who was also working there, walked up to me, stared at me angrily like I had committed a crime, and said (or perhaps he didn't say it, but I heard it in his voice), "Men in our family do not lose control of a shitty little wheelbarrow." I stood there, and after first watching the liquid concrete mix with the wet ground, I looked up and returned my brother's stare with all the intensity I could muster. It wasn't clear to me whether tears were streaming down my face because on that part of the anatomy it can be difficult to separate rain drops from tears. All of a sudden the

[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 18, 2017, in Orlando, FL, USA. The video of the original address can be found at the ASHG website.

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https://doi.org/10.1016/j.ajhg.2018.01.012.

look on my brother's face changed from anger to wonderment, and he pointed to the road that was about 200 m behind me. I turned around and saw that a car had stopped on the side of the road, and out of it stepped a man elegantly dressed in a three-piece suit with a box under his arm. He began to walk toward us, wading through water and mud. When he was about 10 m away from us, he stopped and half shouted with a smile on his face, "Guys, do you want to buy Encyclopedia Britannica?"

In 1996, when I told people that I was leaving my position as a professor at Harvard Medical School to form a biotech company to do large-scale human genetics in Iceland, I was told that it made no sense. If I wanted to do human genetics, I should do it in Boston, which is bursting with talent and great universities. I was told that I would fail because there was no tradition or know-how in the field of human genetics in Iceland. I was told that I was pathologically optimistic. My response was always that if this pathologically optimistic man should fail at human genetics, he could always get a job selling Encyclopedia Britannica.

The truth of the matter is that there was absolutely no tradition or know-how in biomedical research in Iceland in 1996. Therefore, we could not bring anything into deCODE from the outside; it all had to be built on the inside. It was rather difficult but not necessarily bad because the paucity of prior experience gave us more freedom to fashion our own style, which we did.

Early on, we attached a wide-angle lens to our camera, and rather than focus on a collection of specific diseases or other phenotypes, we began to focus on contributing to an understanding of how diversity in the sequence of the genome results in human diversity. Hence, for each and every data point on diversity in the sequence, we tried to obtain as much data as possible on phenotypes of the contributor of that data point. For that purpose, we proposed 20 years ago the construction of a centralized healthcare database in Iceland that would revolutionize the delivery of healthcare in the country, as well as research into the nature of disease. The fundamental idea was to bring genetics into the delivery of healthcare. We were proposing the implementation of what is now called precision medicine many years before anybody else. Over 90% of Icelanders supported the idea, but we ran into difficult opposition that was, in part, fueled by objections voiced by luminaries in the international genetics community who, convinced that they invented the concept, are now busily trying to bring about precision medicine in their own countries. It is nothing short of amazing how much scientists can dislike good ideas if they are not their own, and I am no exception to that. We were, however, unperturbed, and although the idea of a centralized database never became a reality, we have over the past 21 years gathered an unprecedented amount of data on sequence diversity and phenotypes on one and the same population. We have genotyped half of the population with Illumina chips and sequenced the whole genomes of 15% of the nation, we can phase the entire genomes of all Icelanders, and we can accurately impute sequence variants with allelic frequency down to 0.01% into those genotyped. On the way, we constructed a unique database of centuries' worth of genealogy of the entire Icelandic nation, and it has been extremely useful to us. With the help of genealogy, we can infer sequence variants in the genomes of those who have not been genotyped with an accuracy that we can assess and is reasonably good. Hence, we have transparency into the genomes of almost the entire nation. We have contributed to the discovery of sequence variants that associate with a very large number of diseases and other traits, larger than any other group in the world. Some of these discoveries have shed new light on the pathogenesis of diseases and even changed our views of the nature of diseases in a fundamental way. Some of these discoveries have now been turned into promising drug-discovery programs, which in a way is the icing on the cake for an old-fashioned physician like myself. In addition, we have contributed more than most to the study of the generation of new diversity through recombinations, gene conversions, and *de novo* mutations.

Behind the success of deCODE Genetics is a team of unbelievably committed and talented people, the toughest team on Earth. I sincerely hope that the old saying is true that in the end, you are judged by the company you keep, because there is no company in the world like my colleagues at deCODE. Just imagine yourself to be blessed with the opportunity to work for two decades with Augustine Kong, Daníel Guðbjartsson, Unnur þorsteinsdóttir, Patric Sulem, Agnar Helgason, Gísli Másson, Hákon Guðbjartsson, þórunn Rafnar, Bjarni Halldorsson, Simon Stacey, Guðmar þorleifsson, Ingileif Jónsdóttir, and my old graduate student Jeffrey Gulcher, who began this journey with me, to name just a few.

I am going to end these words by addressing Jeffrey Gulcher, my old graduate student and a force of nature, who is a wonderful human being and voted for the current president of the United States and continues to support him.

Jeffrey, we have a manuscript out for review based on the works of Augustine Kong on what he calls genetic nurture, where he quantifies the impact that sequence variants in the half of parental genomes that are not passed on to their children have on the fate of the children. He shows that their effects are substantial on all kinds of phenotypes. Furthermore, he goes on to show that variants in the genomes of siblings but not shared by the proband affect the proband, and so do non-shared variants in the genomes of more distantly related individuals. This shows that, genetically, we are in many ways like ants in an anthill, which are not so much individuals as they are parts of the anthill. We are not islands—we are parts of the main. We are influenced by the genetic attributes of others, and in that way society makes us and shapes us, and in that way we make society. Even when we are different in

some small way, we are part of the same. The fundamental task of human genetics is the study of human diversity, but as we dive into our subtle differences, we are constantly reminded of the qualities that we share. There are, however, groups out there such as white supremacists, those who aspire to erect sky-high walls on borders between countries, those who seek more immigration jails, and those who want to discriminate against people on the basis of the very qualities that have yielded the diversity we want to celebrate and who have the audacity to claim that population genetics is providing them with arguments in support of their repugnant view of the world. We have to protest this abuse of our work loudly and remind our fellow human beings that, genetically, there really are no refugees or illegal aliens or evil Muslims—there are only human beings, who are our brothers and sisters, who were all born equal to us, and whose unique differences contribute to our miraculous diversity. I look at it as my duty as a human geneticist to voice this view of the world, and I expect all of you to do the same.