2015 Curt Stern Award[1]

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Thank you, Elaine, for that wonderful introduction and for all the support from the beginning of my faculty career. It's a tremendous honor to be recognized with the Curt Stern Award by the ASHG, and I'd like to express my gratitude to the Awards Committee for this recognition. An award is really invested with meaning by its past recipients, and I encourage you to take a look at the list of past Curt Stern Award winners. It's a remarkable group of people, many of whom I've had the privilege to know personally. They include mentors and early role models of mine when I was just entering the field, such as David Page and our amazing president, Neil Risch, as well as some of my closest colleagues and friends in genetics. In fact, I once published a commentary[1] with two friends and recent winners of the award, David Altshuler and Mark Daly, and it's a great honor to follow them.

My journey in human genetics began when I was spending a year after graduate school in the Theoretical Physics Department at the University of Oxford and trying to figure out what I wanted to do with my career. In my reading, I came across the now classic paper from Dean Hamer's group,[2] who reported one of the early attempts to apply the emerging techniques of linkage analysis to more complex traits in humans. The analyses in the paper piqued my interest, and I wanted to understand the math behind them. The references pointed me to a series of classic papers by Neil Risch, and these laid out the concepts and mathematics of linkage analysis for complex traits.[3–5] This work totally hooked me and showed me that the quantitative skills I developed as a physicist could be applied to genetics. At about this time, an editorial[6] critiquing the Hamer paper appeared in *Nature*. My very first publication in genetics was a letter to the editor of *Nature*, in which I pointed out that the argument in this editorial was inconsistent with the basic principles of linkage analysis, which I had just learned.[7]

From this point, I decided that I wanted to study genetics of complex traits. I started asking around for people working on this, and someone pointed me to an early paper by Eric Lander on quantitative trait analysis in tomatoes.[8] I read this and other papers by Eric and then managed to talk my way into joining his group at the Whitehead/MIT Center for Genome Research. This was a fantastic place to learn genomics and quantitative genetics.

My first major project grew out of an influential paper by Eric and David Botstein on homozygosity mapping in consanguineous human pedigrees.[9] At around the time I joined Eric's group, David's group was generating data on such pedigrees with Fanconi anemia and wanted to use the principles described in Lander and Botstein to analyze the data.[10] Eric assigned me the task of converting these principles into a working computer program that could handle real data for a dense map of microsatellite markers. It turned out that this required a fair bit of algorithmic development, and I was finally able to crack the computational complexity of the problem by drawing on ideas used in the fast Fourier transform (FFT) algorithm. Mark Daly and I then wrote the code for the program, which was called MAPMAKER/HOMOZ at the time.[11] We subsequently generalized the algorithms and software first for sibling-pair analysis[12] and then for linkage analysis of general human pedigrees; the program is now named GeneHunter.[13] Subsequent work by us and other groups led GeneHunter and related programs to become the standard tools for mapping disease-related genes in human families.

[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 9, 2015, in Baltimore, MD, USA. The audio of the original address can be found at the ASHG website.

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http://dx.doi.org/10.1016/j.ajhg.2016.01.002.

Another key problem at the time was interpretation of results from emerging whole-genome scans for linkage. Such scans faced an extensive multiple-testing problem not present in earlier studies employing one or a few genetic markers. Eric and I used mathematical analysis and computer simulations to develop a set of guidelines for reporting and interpreting linkage results in the context of whole-genome scans.[14] These guidelines have been widely adopted by the genetics community, and they continue to be cited today.

By the mid to late 1990s, the field of human genetics was starting to go through the transition of realizing that linkage studies were not going to be sufficiently powered to unravel the genetics of complex traits and diseases and that population studies were going to become increasingly important. At the time, there was a lively debate around the number of SNPs that would ultimately be required for what are now known as genome-wide association studies (GWASs). Although it was clear that the question would eventually need to be answered empirically,[15] the necessary data did not exist at the time. In order to provide some insight, I carried out population-genetics simulations with the best available parameters and proposed that the answer would turn out to be around half a million SNPs.[16] At the time, the total number of SNPs known in the genome was a few thousand, and large-scale genotyping techniques were just beginning to be developed.[17] As a result, the estimate of half a million SNPs was highly controversial.[18] However, large-scale SNP-discovery efforts by the SNP Consortium and then by the HapMap Project, as well as commercial development of SNP genotyping arrays, made studies on this scale practical, and the first well-powered GWAS did indeed use roughly half a million SNPs.[19] Of course, studies with much larger numbers of SNPs are routine today. For more on the history of GWASs, see Kruglyak.[20]

My early career in genetics focused on developing study designs and computational methods that enabled others to answer scientific questions. When I started my own lab at the Fred Hutchinson Cancer Research Center, I wanted to also try asking and answering such questions myself. With support from Lee Hartwell, Elaine, and others at the Hutch, I was able to start a wet lab focusing on studying the genetics of complex traits in a simple and powerful model system: the yeast *Saccharomyces cerevisiae*. Specifically, I had the idea that global measurements of gene expression, made possible by the then new microarray technology, could be treated as quantitative trait phenotypes for linkage analysis in the same way as more traditional organismal traits. I worked with two fantastic postdocs, Rachel Brem and Gael Yvert, to carry out the first of what are now known as expression quantitative trait locus (eQTL) studies.[21] This paper introduced a number of now standard concepts and approaches for eQTL analysis, including polygenic inheritance of expression levels, the distinction between *cis* and *trans* eQTLs, and the existence of eQTL hotspots that affect the expression of many genes. Today, eQTL analysis is a widely used tool in human disease genetics and beyond.[22]

Since then, my group has been focused on continuing to use simple model organisms to gain insights into complex problems motivated by human genetics. One key focus in the community recently has been the problem of missing heritability.[23] Working in yeast, we have been able to show that in a well-powered study, we can detect loci that capture nearly all of the estimated additive heritability of a trait.[24] More recently, we examined the contribution of genetic interactions to quantitative trait variation.[25] Although the genetic architecture of complex traits is by no means a solved problem, converging insights from our work in yeast and from human genetics suggest that most quantitative trait variation is explained by a largely additive model wherein very large numbers of contributors have small individual effects.

My love of genetics is perhaps best illustrated by the following anecdote. When I applied for a career-development award to retrain from physics to genetics, I received a very positive set of reviews, but the reviewers had one concern:

> Dr. Kruglyak's academic history indicates frequent and wide shifts in interest. This characteristic can be viewed as either a strength or a weakness but nevertheless one that evokes the question of how long Dr. Kruglyak will remain interested in this area.

This is a polite way of saying that I am easily bored, and those who know me would agree that this is accurate. It's been a privilege to work in a field where the questions are so rich and the technology evolution is so rapid that you can be constantly learning and doing new things. My interest in genetics hasn't waned one bit, and I look forward to continuing to unravel the puzzles of genetic complexity in the years to come.

I'd like to conclude by once again thanking all the mentors, collaborators, and members of my lab, without whom I wouldn't be standing here today.

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