# Correction

**PROFILE**

Correction for "Profile of Aravinda Chakravarti," by Tinsley H. Davis, which was first published May 6, 2019; 10.1073/pnas.1906109116 (*Proc. Natl. Acad. Sci. U.S.A.* **116**, 10608–10610).

The editors wish to note that on page 10609, Dr. C. C. Li was described as a founder of the field of population genetics. However, Dr. C. C. Li's impact on the field was as an influential figure rather than as a founder.



Published online July 1, 2019.

www.pnas.org/cgi/doi/10.1073/pnas.1910566116

PROFILE

# Profile of Aravinda Chakravarti

**Tinsley H. Davis,** *Science Writer*

Many of the genetic variations uncovered by genome-wide dragnets are bycatch, not primary disease culprits. Separating causality from coincidence in this sea of data is challenging, especially when many of the candidates do not reside in the coding portion of the genome. Aravinda Chakravarti, director of New York University's Center for Human Genetics and Genomics, has made a career of not just cutting through the noise but anticipating it, thanks to his training in statistics and genetics. In his Inaugural Article, Chakravarti, who was elected to the National Academy of Sciences in 2015, outlines a systematic process for determining causality in genome-wide association studies. He examines variants of regulatory elements that control gene expression by focusing on variation in *cis*-regulatory elements that target the *SCN5A* gene, which is implicated in sudden cardiac death (1).

**Aravinda Chakravarti. Image courtesy of Sumantra Chatterjee (New York University School of Medicine, New York).**

## Finding Direction

Born in Calcutta, India in 1954, just seven years after the country gained independence, Chakravarti remembers a mood of optimism and a sense of possibility. "I grew up in India at a very magical time." Only in hindsight would Chakravarti call his family's financial circumstances poor. "I had every kind of material to read, from national newspapers to glossy magazines to books," he says. "I grew up in a house where reading was very valued, and curiosity was valued."

Chakravarti attended a local high school run by Methodist missionaries that offered advanced science courses. After high school, Chakravarti applied to a plethora of colleges. "I don't know that I had a particular sense of direction," he says. That changed as soon as Chakravarti saw the first page of the Indian Statistical Institute's entrance examination, which contained two 10-digit numbers. The question asked which of five possible answers resulted from multiplying the two numbers. "It was obvious that the answer could not be deduced by arithmetic—there was no time—but logic," says Chakravarti. "In India, the ability to advance is the ability to take tests, but that's not how science advances." The entrance examination hinted that his soon-to-be alma mater "valued thinking and logic."

During his time at the institute, Chakravarti received a solid grounding in science and published his first two papers, one of which examined petal distribution in composite flowers and the relation to the Fibonacci sequence, an exercise that required counting the petals on more than 6,000 flowers (2). The experience and mentoring he received encouraged Chakravarti.

Chakravarti was deeply influenced by his training. "We were not taught statistics as a tool as it is today. We were taught statistics as a way of thinking." True applications of statistics, he says, "require you to know the domain to which you apply it," and it was from that line of reasoning that Chakravarti sought further training in human genetics after graduating in 1974. "I left with a sense of purpose."

Chakravarti decided to leave India for a doctoral program in the United States, recalling the advice of visiting Australian geneticist Robert Kirk, who had told him that India would continue to be outpaced in the field. "And this was all before recombinant DNA, let alone the Human Genome Project," he says.

Most human genetics programs recruited only medical degree holders, and Chakravarti wanted the broad laboratory training that most doctoral epidemiology programs would not provide.

The relatively new University of Texas Health Science Center at Houston's Graduate School of Biomedical Sciences provided this opportunity. There, Chakravarti



This is a Profile of a recently elected member of the National Academy of Sciences to accompany the member's Inaugural Article on page 10636.
Published online May 6, 2019.

studied with population geneticist Masatoshi Nei and relished the laboratory work. "At that point in time, I was learning the technical details. We didn't worry about jobs or grants, we just did research," he says. "It was really just extending my childhood." During that period, he also published a cookbook, *Not Everything We Eat Is Curry: A Bengali Guide to Indian Cuisine*, and married biochemist Shukti Chakravarti (3).

Chakravarti's childhood—but not his passions for his family and cooking—came to an end with graduation in 1979 and a short-lived postdoctoral position at the University of Washington, where he worked on demographic genetics and large datasets. "It was big data for those days, with intense computing," he says. "You'd laugh at the computers now." However, the experience was not quite what Chakravarti wanted.

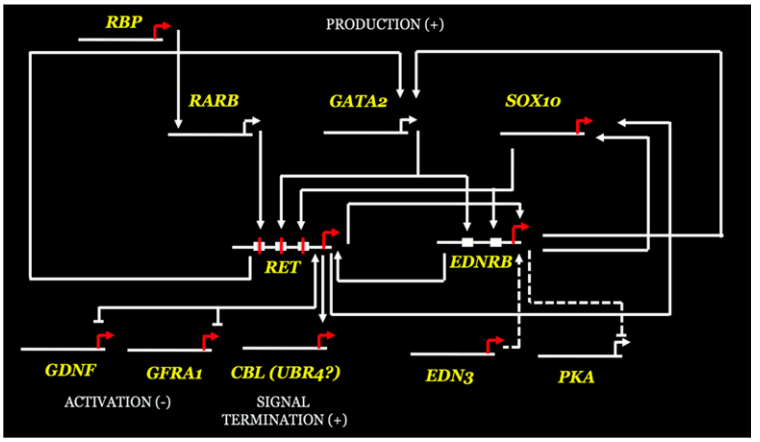
## Getting a Handle on Things

In 1980, Chakravarti took a teaching job at the University of Pittsburgh Graduate School of Public Health. He was responsible for six courses a year. He initially had no office or staff, and had to go to the computer center to enter and analyze data. However, the time proved fruitful. He worked with preeminent population geneticist C. C. Li, a founder of the field, and began a collaboration with Haig Kazazian and Stylianos Antonarakis to understand the molecular diversity of the β-globin gene cluster in humans, eventually identifying a hotspot for recombination (4).

Using population genetics to predict the disease state of individuals intrigued Chakravarti. Since 1978, when the sickle cell mutation was shown to be associated with a noncoding polymorphism in DNA, he had imagined that the association, called linkage disequilibrium, could be used to map mutations in reverse. Outliers, alleles that associate at rates higher than random assortment, could predict disease and provide the foundation for his work.

By the late 1980s, Chakravarti wanted to apply the concept of linkage disequilibrium to a disease whose genetic underpinnings were unknown. "The genes cloned at the time had a lesion, deletion, or translocation at the disease locus, which was used as a handle for getting at the gene." Cystic fibrosis had no such handles, but Chakravarti was convinced its high prevalence in the population was indicative of selection, and thus the key to the problem. "There's no way you could have selection without inducing strong linkage disequilibrium." Chakravarti's hunch was correct, and before long, his team published the positional location of CFTR using this principle (5). "That was the first success in mapping a common disease allele in a general—not isolated—population," says Chakravarti.

In addition, the marker maps created to solve the cystic fibrosis problem and detect the alleles' mutual association (i.e., haplotypes) prompted Chakravarti's role in the eventual creation of the International HapMap Project, where he served on the steering committee from 2002 to 2007, as well as his eventual contributions to the 1000 Genomes Project (6). Both are projects that aim to catalog human genetic variation for phenotypic mapping. For Chakravarti and other human geneticists, it is genetic variation and its association that ironically provide both the power to map and the potential to confound causal and irrelevant factors.




**Network of regulatory genes underlying Hirschsprung disease. Such networks are thought to underlie other complex traits and disorders. Image courtesy of Aravinda Chakravarti and Sumantra Chatterjee (New York University School of Medicine, New York).**

## Meeting Serendipity

To sort through the genetic noise, Chakravarti has relied on a de facto model disease. Chance led Chakravarti to begin studying Hirschsprung disease in 1988 after listening to an account of a debilitating congenital disorder that prevents proper innervation of the intestinal tract. What he heard did not sound like either a multifactorial or Mendelian disease, and he thought, "Maybe what I should do is to devise methods for studying such complicated non-Mendelian disorders."

The challenges would be vast. "We didn't know at what resolution we needed to develop markers," he says. "It wasn't like you could look them up." When David Kupfer, chair of the psychiatry department, asked Chakravarti to study mood disorders instead, Chakravarti agreed to consult if Kupfer provided laboratory space for his Hirschsprung disease studies. "He gave me the gift of a career."

Chakravarti learned how to do family studies, beginning with Old Order Mennonite populations, and he now feels a kinship with what he refers to as "his" families. "These are not families that we simply get data on. We communicate with them, and when they have problems, I'm not an MD, but I make a point of connecting them with experts."

In 1993, his work mapped one of the major genes, *RET,* for Hirschsprung disease, which encodes a tyrosine kinase receptor (7). Much of the overall genetic variation in *RET* was not in the coding areas, but it was not until years later that these variations would be revealed in its enhancers, noncoding genetic elements that affect the expression of *RET* (8).

Today, after 28 years of research and at least 24 genes so far implicated in its cause, the heritability of Hirschsprung disease is mostly, but not fully, explained, according to Chakravarti. "We are using these lessons for more complicated disorders," he says. "It never

ceases to amaze me what a single model system can teach you. I believe that we have to first choose systems that can really illuminate features that we want to learn. Databases and knowledge are not the same thing."

While he was director of the Center for Complex Disease Genomics at Johns Hopkins University in 2015, Chakravarti identified a rare genetic cause of autism by studying families in which females were severely affected (9). In addition to these two congenital conditions, he focused on two genetically complex adult-onset conditions: hypertension, having identified more than 150 genetic contributors over the years (10), and sudden cardiac death (11). The heart rhythm's QT interval is physiologically determined, and intervals that are too short or too long can lead to problems. In his Inaugural Article, Chakravarti focused on the genetic control of this physiological process, determining that eight of the 13 *cis*-regulatory gene variants identified by a genome-wide association study are causal, implying that they affect regulation of *SCN5A* (1).

Throughout his career, Chakravarti has held positions in departments as diverse as anthropology, biostatistics, and psychiatry. However, there are two scientific disciplines that he considers of particular relevance to human societies. "Socially, I am a complete egalitarian, but of all the biological sciences, even today, I think two of the greatest of public interest are genetics and neuroscience," he says noting that they come with high public relevance and ethical responsibilities.


**1** Kapoor A, et al. (2019) Multiple *SCN5A* variant enhancers modulate its cardiac gene expression and the QT interval. *Proc Natl Acad Sci USA* 116:10636–10645.
**2** Majumder PP, Chakravarti A (1976) Variation in the ray and disk florets in four species of compositae. *Fibonacci Quart* 14:97–100.
**3** Chakravarti A, Morizot DC (1978) *Not Everything We Eat Is Curry: A Bengali Guide to Indian Cuisine* (Harold House, Houston).
**4** Chakravarti A, et al. (1984) Nonuniform recombination within the human beta-globin gene cluster. *Am J Hum Genet* 36:1239–1258.
**5** Kerem B, et al. (1989) Identification of the cystic fibrosis gene: Genetic analysis. *Science* 245:1073–1080.
**6** Abecasis GR, et al.; 1000 Genomes Project Consortium (2012) An integrated map of genetic variation from 1,092 human genomes. *Nature* 491:56–65.
**7** Angrist M, et al. (1995) Mutation analysis of the RET receptor tyrosine kinase in Hirschsprung disease. *Hum Mol Genet* 4:821–830.
**8** Emison ES, et al. (2005) A common sex-dependent mutation in a RET enhancer underlies Hirschsprung disease risk. *Nature* 434:857–863.
**9** Turner TN, et al. (2015) Loss of δ-catenin function in severe autism. *Nature* 520:51–56.
**10** Ehret GB, et al.; CHARGE-EchoGen consortium; CHARGE-HF consortium; Wellcome Trust Case Control Consortium (2016) The genetics of blood pressure regulation and its target organs from association studies in 342,415 individuals. *Nat Genet* 48:1171–1184.
**11** Arking DE, et al. (2006) A common genetic variant in the NOS1 regulator NOS1AP modulates cardiac repolarization. *Nature Genet* 38:644–651.