

## Luigi Luca Cavalli-Sforza (1922–2018)

The political map of the world has sharp boundaries. The genetic map of the world has no sharp boundaries. The frequencies of most gene-variants in humans show a near-continuous variation, with virtually no sharp changes, across global geographical space. This was a seminal insight that we have obtained from the systematic and painstaking work carried out over a period of about four decades by Luigi Luca Cavalli-Sforza, who passed away on 31 August 2018, at the age of 96 years.

Luca (as many of us called him), went to medical school in Pavia (Italy) and graduated in 1944. He disliked medical practice. He joined the group of Sir Ronald A. Fisher in Cambridge in 1949, as an Assistant in Research. In Cambridge, he worked on the genetics of *E. coli*, which at the time was a new field. He isolated a mutant strain of *E. coli* that he and others would later use to discover and clarify the nature of ‘bacterial sex’ (conjugation). While in Cambridge, he had established collaboration with Joshua and Esther Lederberg. Over the next eight years, Luca and the Lederbergs published definitive results on conjugation. He returned to Italy in 1950 initially to a Milan pharmaceutical company and soon after joined the University of Parma. The topography of the region around Parma was mountainous. The villages in the mountain valleys were small and isolated. In these villages, people mostly married their relatives within the villages. The villages in the plains were relatively larger and connected. Outbreeding was common in these villages. R. A. Fisher had theoretically worked out that the main consequence of small size of a population was that variation in the frequency of a gene variant will fluctuate unpredictably from one generation to another; a phenomenon not observed in large populations. Luca empirically demonstrated that this was true through his systematic studies on blood group frequencies in the villages of the mountain valleys and plains of Parma. He made a name for himself as a teacher and a geneticist. He joined (I have heard that he was invited to join) Stanford University in 1970 as a Professor and worked there until 1992.

He went to Africa and carried out important genetic studies, notably among

the hunter–gatherer Pygmy. From 1966 to 1985 he visited Africa 11 times for varying lengths of time to study the Pygmies and other tribes. His experience with the Pygmies, who had a completely different lifestyle but were genetically like his ‘brothers, really’ (as recorded in a video interview), got him thinking ‘why could I not trace humanity’s spread across the planet?’ Cavalli-Sforza and Anthony Edwards presented the first evolutionary



tree of 15 human populations in the 11th International Congress of Genetics, The Hague, in 1963, based on gene frequency data for five blood group systems, using a combination of least-squares and parsimony methods. In fact, Cavalli-Sforza and Edwards had provided, in a series of papers published in 1963 and 1964, statistical methods of estimation applied to stochastic models of evolution and novel methods for computing evolutionary trees from genetic data. Later, in 1994, Luca and his colleagues<sup>1</sup> published an updated evolutionary tree based on 42 global populations and 49 polymorphic genetic marker systems.

Luca was not just interested in documenting patterns of variation of frequencies of gene variants. He was really looking for *processes* that resulted in the patterns. These processes were mostly associated with movement of people because of, and often along with, some cultural and demographic phenomena. While studying patterns of variation of genetic markers in Europe, Cavalli-Sforza identified gradients of frequencies. He and the eminent archaeologist, Albert Ammerman, proposed a radically new hypothesis for the peopling of Europe. The prevailing belief was that modern Europeans were descended largely from the continent’s Stone Age inhabitants, who replaced the Neander-

thal people starting about 40,000 years ago. Cavalli-Sforza with Ammerman<sup>2</sup> proposed, based on the direction of gradients of gene frequencies and timing of certain past events, that Europeans are descended largely from populations of farmers who started migrating out of the Middle East 9,000 years ago. As the sons and daughters of farming families left their parents’ farms and moved into new territory, they interbred with the existing hunter–gatherer populations, which produced gradients of genetic change radiating from the Middle East. Some detailed aspects of their results have been modified in later genetic studies on European populations using data on a far larger number of gene variants.

Luca collaborated with Madhav Gadgil and generated some fine data on mitochondrial DNA of three caste and tribal groups of India. Analyses of these data showed that the pattern of genetic affinities of the three groups did not correspond well with their social affinities/ranks. Their genetic data provided insights on the demographic histories of the three populations. These results were published in 1995 in the *American Journal of Human Genetics*.

I first met Luca during the 1981 annual meeting of the American Society of Human Genetics. I had corresponded with him earlier when I was doing my Ph D work on patterns of variation in blood group frequencies in India, during 1977–1980. Later, I also had the opportunity to collaborate with Luca to examine issues pertaining to the introduction and spread of modern agriculture in India. Using a large number of Y-chromosomal markers we, together with Luca and some members of his group in Stanford, were able to show that modern organized agriculture was brought into India by farmers moving from the Fertile Crescent region, possibly displacing the rudimentary forms of agriculture that were then prevalent in India.

Luca’s dream was a worldwide project to discover and understand the patterns of variation in gene frequencies, and to interpret these patterns in the light of human ancestries and movements resulting from demographic and cultural pressures. He called this the Human Genome Diversity Project (HGDP), which he championed. However, the project could

never be initiated in the global form in which it was conceived. It ran into rough weather. Six of us, me included, who rallied behind him, appealed to UNESCO to provide us a hearing. UNESCO formed a seven-member working group, comprising members of the International Bioethics Committee, to produce a report based on our presentations at a special meeting of the UNESCO in 1994. The scientific aims of HGDP were<sup>3</sup>: (a) to investigate the variation occurring in the human genome by studying samples collected from populations that are representative of all of the world's peoples; and, (b) to create a resource for the benefit of all humanity and for the scientific community world-wide. The resource will exist as a collection of biological samples that represents the genetic variation in human populations world-wide and also as an open, long-term, genetic and statistical database on variation in the human species that will accumulate as the biological samples are studied by scientists from around the world. We felt that the main scientific values of HGDP are: (a) deepening our understanding of human history and identity; (b) gaining knowledge about the environmental and genetic factors involved in predisposition and resistance to disease, so-called genetic epidemiology; and (c) encourage the development of local laboratories where the collection of genetic samples will be collected and analysed. In 1995, UNESCO turned down the HGDP's proposal for UNESCO to become 'international patrons' of the Project. The Working Group's Chairman<sup>4</sup> wrote: (a) the scientific goals are generally valid, (b) the goal of the Project to understand human history is controversial because of *feared misuse* (emphasis mine), but the possible medical goals seem to be universally accepted; (c) the goal of reducing racism is the most debatable claim of the HGDP, and it will be impossible to provide any proof that it will or will not happen until after the event. Luca was a known crusader against racism. In 1973, he publicly debated his Stanford colleague and Nobel laureate William B. Shockley, who had gained notoriety for declaring that blacks were less intelligent than whites. In his book *Genes, Peoples and Languages*<sup>5</sup> he wrote 'Racism should be condemned because its effects are pernicious'. HGDP could never be undertaken

on the scale that he had planned. He had hoped to organize collection of 10,000 samples from around the world, but was able to sporadically collect about 1,000 samples from some 50 populations. Samples are stored in Paris at the Center for the Study of Human Polymorphisms (CEPH); many samples have been transformed into cell-lines and have become a valuable resource for population genetic studies.

With his Stanford colleague Marcus Feldman, Luca made deep contributions to cultural evolution. They provided a framework and a suite of methods to study – similarly as for genetic characteristics – the transmission and evolution of language, values, customs and other social characteristics. Their work culminated in the publication of their joint book *Cultural Transmission and Evolution: A Quantitative Approach*<sup>6</sup>.

Cavalli-Sforza wrote<sup>7</sup> 'Most patterns (of gene frequency variation) found in the analysis of human living populations are likely to be consequences of demographic expansions, determined by technological developments affecting food availability, transportation, or military power. During such expansions, both genes and languages are spread to potentially vast areas. In principle, this tends to create a correlation between the respective evolutionary trees. The correlation is usually positive and often remarkably high.' He empirically showed this<sup>7</sup>. 'It was exciting to discover that we had confirmed a conjecture made by no less a pioneer than Charles Darwin ... that if the tree of genetic evolution were known, it would enable scholars to predict that of linguistic evolution,' he wrote<sup>8</sup>.

He authored many books. *The Genetics of Human Populations*<sup>9</sup>, written jointly with Walter Bodmer, made human population genetics 'finally come of age as a distinct science as opposed to biochemical, clinical or other fields within genetics', wrote Frank Livingstone, an eminent physical anthropologist [<https://onlinelibrary.wiley.com/doi/abs/10.1002/ajpa.1330390117>]. A sequel was published by Bodmer and Cavalli-Sforza in 1976 (ref. 10). He was a wonderful popular science writer as well; in 2001 he wrote *Genes, Peoples and Languages*<sup>5</sup> and in 1995 he wrote *The Great Human Diasporas*<sup>11</sup> with his film-maker son, Francesco.

Cavalli-Sforza was an elected Fellow of The Royal Society and an elected Member of the US National Academy of Sciences. He was awarded the Mendel Medal in 2002.

Luca served on the Council of Scientific Advisers of the International Centre for Genetic Engineering and Biotechnology (ICGEB) from 1985 to 2005, and came to ICGEB, New Delhi, for Council meetings.

Luca firmly believed that by studying co-evolution of biological and cultural characteristics of man, he could trace the origins of humanity. And, he largely did. He also stated<sup>11</sup>, 'I will be the first to disbelieve my own ideas if a scientific discipline points in a different direction'.

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