

## Masatoshi Nei (1931–2023)

By Jianzhi Zhang & Sudhir Kumar

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**Evolutionary geneticist whose powerful statistical methods facilitated the molecular revolution of evolutionary biology.**

If you study evolution, chances are that you have used Nei's distance to measure the genetic difference between populations of your favourite organisms, the neighbour-joining method to reconstruct the phylogenetic relationships among various species and/or the Nei–Gojobori method to compute rates of synonymous and nonsynonymous nucleotide substitutions for testing natural selection acting on gene sequences. Masatoshi Nei – the architect of these, and many other, powerful methods for studying molecular population genetics and evolution – died on 18 May 2023, at the age of 92.

Nei was born on 2 January 1931 to a family of Japanese farmers. He lost vision in his left eye at the age of 15 owing to an accident, which led to a reduction in physical activities and a focus on academic studies. Nei received a bachelor's degree in genetics from Miyazaki University and master's and doctoral degrees in quantitative genetics from Kyoto University, which were followed by postdoctoral training at University of California, Davis, and North Carolina State University. From 1962 to 1969, Nei worked on a series of population genetics problems at the National Institute of Radiological Sciences, Japan. During this time, he often visited the great population geneticist Motoo Kimura at the National Institute of Genetics in Mishima, Japan. It was in 1968 that Kimura proposed the neutral theory of molecular evolution, which asserts that most intra- and inter-specific differences in protein-coding DNA sequences are selectively neutral and not adaptive. For the next half of a century, Nei wholeheartedly defended and further developed the neutral theory. He considered himself a protégé of Kimura.

Nei moved to the USA in 1969 to become a professor at Brown University (1969–1972), which was followed by appointments at University of Texas Health Science Center at Houston (1972–1990) and Pennsylvania State University (1990–2014). He created a world-leading Institute of Molecular Evolutionary Genetics at Penn State, where



we joined his research group as graduate students. After retirement in 2014, Nei was an adjunct professor at Temple University until his death.

In a career spanning over six decades, Nei wrote five books, edited two volumes and published over 300 papers. These works have had tremendous impacts not only on population and evolutionary biology, but also on systematics, human genetics, comparative genomics, conservation biology and more. One measure of impact is citations in scientific publications. His work has garnered over 400,000 citations, and 11 of his publications have each received over 10,000 citations. One of us (J.Z.) once asked him whether he could predict at the time of writing whether a paper would be a blockbuster. He answered no. He mentioned treating every manuscript as a potential blockbuster – ensuring that it is accessible to all potential readers, and not only a small circle of colleagues.

Despite being a theoretician for most of his research life, Nei very much appreciated the power of experimental molecular biology in answering evolutionary questions. For decades, his group was frequently among the first to develop statistical methods for analysing the next type of molecular data on the horizon

– be it protein electrophoresis data, restriction fragment length polymorphism data, microsatellite data or DNA sequence data. The statistics he invented are usually simple by design but have clear biological meanings, and so are liked by biologists.

For instance, Nei's standard genetic distance between two populations is expected to be proportional to the time of divergence between the populations under the influences of mutation and drift, so it is useful for inferring population divergence times. Another example is the neighbour-joining method for inferring phylogenetic trees, which is a heuristic version of the theoretically more rigorous minimum evolution method. Nevertheless, neighbour-joining performs well and is fast, so has greatly facilitated the popularization of phylogenetic analysis across multiple disciplines. In the early 1990s, one of us (S.K.) initiated the development of the software package MEGA with Nei and Koichiro Tamura. Nei provided statistical guidance, an encouraging scientific environment and financial support for developing the first version of MEGA to make molecular evolutionary genetic analysis accessible to computational and experimental biologists alike. Now in its 11th version, MEGA has been downloaded almost 3 million times.

Apart from developing statistical methods, Nei analysed many types of data to understand the roles of mutation, drift and selection in evolution. For example, in 1976, his group analysed all available data of allele frequencies measured by protein electrophoresis, reporting that the relationship between the mean and variance of single-locus heterozygosity matches the prediction of the neutral theory reasonably well. Although their observation may also be explained by some complex forms of selection, the neutral theory provides a simpler explanation.

Neutralists predict that functionally more important genes or parts of genes evolve slower than functionally less important counterparts, but selectionists predict the opposite – because, in their view, most nucleotide substitutions are driven by positive Darwinian selection, which should be stronger on functionally more important genes or parts of genes. In 1981, by showing that the evolutionary rates of three pseudogenes (relics of past

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functional genes that are no longer functional) are extremely high, Nei and colleagues provided strong evidence for the neutral theory.

Although it requires that most nucleotide substitutions are selectively neutral in gene evolution, the neutral theory allows adaptive substitutions in a small fraction of genes. Searching for genes that experienced adaptive evolution is now a routine analysis in research articles that report new genome sequences, because it provides insights into organismal adaptations and the underlying molecular basis. This practice can be traced back to a 1988 study by Hughes and Nei on human major histocompatibility complex genes, in which they provided perhaps the first DNA sequence-based evidence for positive selection by comparing synonymous and non-synonymous nucleotide substitution rates. Although today selection tests are more complex and claim higher power, the basic idea remains unchanged.

Nei emphasized the role of mutation and drift in evolution throughout his career. Differing from most biologists (who view natural selection as the most important force that drives evolution), he considered mutation to be central. In his view, mutation is the primary force of nature and selection is a secondary

process because it needs the genetic variants produced by mutation. The advocacy of mutation's central role in evolution was the topic of his last major book, titled *Mutation-Driven Evolution* (2013).

As a pioneer in molecular evolution, Nei (along with Walter Fitch) founded the Society for Molecular Biology and Evolution, a vibrant society that now has thousands of members, and *Molecular Biology and Evolution*, a premier journal in molecular and genome evolution. As such, he also helped to establish the infrastructure for the molecular revolution of evolutionary biology.

Both of us have been asked about our experience as Nei's students. Nei was passionate for science and enthusiastic about new scientific developments. He worked hard and had a deep understanding of biology, and he expected us to do the same. Nei was meticulous in research studies and taught us to be critical of the literature. He held strong, well-justified opinions that rarely changed. He trained his students and postdoctoral researchers to write clearly and concisely. He encouraged us to be independent thinkers. He was a generous mentor, as both of us published several articles independently of him while we were his graduate students. Nei's legacy lives on in his mentees,

many of whom are now leaders in various fields of biology.

For his path-breaking research, Nei received many honours, including (for example) the Kyoto Prize in Basic Sciences, the International Prize for Biology, the Thomas Hunt Morgan Medal, the John Scott Medal and membership in the US National Academy of Sciences.

Dr Nei, as he is referred to by colleagues and trainees, will be sorely missed.

## Additional information

J.Z. and S.K. were PhD students under Nei's supervision in the 1990s. S.K. was also a postdoctoral researcher with Nei.

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## Competing interests

The authors declare no competing interests.