

Impact Objectives

- Study human population genetics and molecular evolution of various genome sequences
- Explore the genomic and biological basis for the difference in self-consciousness between humans and primates
- Uncover the origins and formation of the Yaponesian people to understand more about modern Japan

Sequencing ancient history

Professor Naruya Saitou talks about his research into genomics and the history of the Yaponesian people which straddles archaeology, linguists and genomics



Professor Naruya Saitou



Dr Timothy A Jinam

How did you come to be involved in this field of research?

NS: I received my BSc and MSc majoring in physical anthropology from the University of Tokyo in 1979 and 1981, respectively. I was already seeking to fuse natural science and social science from that time. However, I was fascinated by the neutral theory of molecular evolution, and joined Professor Masatoshi Nei's group at Houston, USA, as a PhD student from 1982 to 1986. One chapter of my PhD thesis was a proposal for the Neighbor-Joining method for the construction of phylogenetic trees. After receiving my PhD, I returned to Japan and again studied physical anthropology between 1987-1991 at the University of Tokyo, initially as post-doctorate student, and later as assistant professor. I visited southern and northern China during this period to study various ethnic minority groups there. In 1991, I joined DDBJ (DNA Data Bank of Japan) at the National Institute of Genetics

as an Associate Professor. I was promoted to Professor of population genetics in 2002, which is my current position. I continue to study human population genetics and molecular evolution of various genome sequences.

Can you talk a little about how your research integrates biological studies with humanity and social science studies?

NS: Sciences are divided into many research fields. However, natural phenomena are in fact all connected, and in my view, all sciences, irrespective in natural sciences, social sciences or humanities, should be united. Fortunately, I have a broad interest in many biological and human activities, partially because of my anthropology background. My first original paper was on surname distribution in Japan, and I used various statistical methods to analyse surnames using computer programs. I believe all data, either DNA sequences, linguistic data, or archaeological data, can be analysed in a similar way.


What types of obstacles do you face in your research?

NS: Genome sequencing was very costly for a long time, so I had difficulty securing appropriate funding for sequencing various

organisms. I once collaborated with a RIKEN group who were interested in sequencing chimpanzee genomes. Although only 1 per cent of the whole genome was determined, our paper was published in *Nature* in 2004. Another challenge is collaboration with archaeologists and linguists. Fortunately, I had close contact with some linguists for 30 years, and nowadays I am often invited to linguistics conferences. Generally, linguists are more open minded than archaeologists, who are mostly interested in archaeological evidence. We try our best to integrate these different research fields with genomics. Dr Timothy A Jinam, Assistant Professor in my laboratory, is playing a major role in analysing human genome data in our group.

You have a particular interest in primate and human evolution. What are the goals and aims for your research?

NS: Since my childhood, I have been fascinated by the concept of 'self' and self-consciousness. Monkeys and apes also have their self-consciousness, but human self-consciousness seems to be clearly different from primates. I hope to find the genomic and biological basis of this difference in terms of self-consciousness. This is my ultimate goal. ●



The origins of the Japanese

Researchers at the **Population Genetics Laboratory** in Mishima are uncovering the nature and formation of the Yaponesian people's ancient past and trying to understand the origins of those that make up modern Japan

To understand our origins and history is a fundamental urge for all people. For as long as history has been recorded, people have created stories and myths about their origins and ancestry. This has not changed to this day. The difference now, however, is that we have the resources and technical skills to map out tens of thousands of years of history. The ebb and flow of human migration across planet Earth can be probed with advanced archaeology, linguistics, anthropology and genomics. Together, these can provide a convincing picture of the various divergences and convergences of different human populations across vast areas. In particular, it is possible to better understand how, why and where a particular group or society arose.

Whilst each of these fields have contributed towards this grand picture of human evolution and migration, few attempts to synthesise all these approaches together have been made. Indeed, there is often a certain antagonism between the different areas of expertise. Naturally, it is practically impossible to be an expert in all the areas. However, there is certainly room for researchers looking to bridge the gaps. In fact, this is essential if a full and accurate picture is to emerge, because a conclusion drawn by one of the disciplines alone would be incomplete without information from one of the others. Therefore, it is extremely important that there is work carried out that links these diverse fields.

A FOCUS ON DNA

Professor Naruya Saitou of the Population Genetics Laboratory at the National Institute of Genetics in Mishima has dedicated his career to this synthesis of disciplines. Having initially studied physical anthropology, he completed his PhD in genetics. Since then he has worked in anthropology but primarily in the context of population genetics and molecular evolution. Saitou has worked in many different areas and with many different fields since then.

His most recent work has been a focus on human genome-wide SNP data and using this to understand the history and evolution of the Japanese Archipelago. 'I have been interested in the molecular basis for macroscopic morphological characters, and am convinced that evolutionarily-conserved noncoding sequences (CNSs) are clues given that the majority of these CNSs are now known to be involved in gene expression,' highlights Saitou. 'Another different aspect in my research topic is development of new methods for molecular evolutionary studies.'

UNITING DISPARATE DISCIPLINES

Saitou has been involved in a myriad of projects over a long career. However, his focus in recent times has been on understanding the origins and formation of the Yaponesian people. This broad term was coined by writer Toshio Shimao in 1960s to encompass the diverse peoples of the

Japanese Archipelago over its many thousands of years of inhabitation. This vast project has encompassed many different branches such as genomics, anthropology, archaeology and linguistics. At the same time, he and his team are experts on genomic comparison and are constantly developing new ways to analyse and understand genomic data.

Whilst this project has been a part of Saitou's interests for many years, it is only in the last decade or so that genome sequencing has made the scale of his ambitions possible. 'Although we have been sequencing genomes for several decades now, the last 10 years has seen a steep drop in the cost of this process,' he comments. 'This has made large-scale genetic studies of both modern and ancient genomes a real possibility.' In turn, this opens new avenues towards understanding a population's likely origins and potential insights into migratory phenomena that may have occurred at different times.

TWO GREAT WAVES

Saitou's work on the genetic diversity of the Japanese Archipelago has been able to pinpoint two key migratory events in the history of Japan. The first inhabitants of the islands were the Jomon peoples - hunter-gatherers who dominated the islands until around three thousand years ago. Saitou and his team have found a relatively low percentage of their DNA in the populations of modern Japan. However, the similarity ►



is much higher with the inhabitants of Hokkaido and Okinawa - the northernmost and southernmost regions. The inhabitants of these islands - the Ainu and Ryukyans - have long assumed to be different from mainland Japanese populations. This was due to morphological and linguistic differences between the populations.

The rest of the genetic make-up of the Japanese population is derived from a second wave of migration - the Yayoi. These

genes. But genetics also play a key role in altering the likelihood of a huge range of other diseases.' Everything from heart disease to gut diseases and neurological issues all have a strong genetic component. However, whilst a genetic link has been established and, in some cases, specific genes identified, in many more cases the nature of the genetic link is unclear. 'Therefore, sequencing and analysing more genomes will help provide more information about the links between genetics and health,' he continues. 'In particular, it has long been

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migrants arrived from somewhere on the East Asian mainland and brought agriculture to the archipelago. 'The exact timing of the migration is disputed; however, it appears to have started between 3 and 2.5 thousand years ago,' confirms Saitou. 'In addition to agriculture, they also brought a range of novel technologies as well as a new language.' He explains that their DNA lineage is by far the most dominant in all Japanese populations. The DNA evidence, therefore, supports and compliments the archaeological and linguistic evidence that suggests these two major migratory events in Japanese history.

MODERN USES OF ANCIENT HISTORY

The results of Saitou's Yaponesian project are already proving interesting and helping to uncover Japan's ancient past. However, as more genomes are sequenced and the different genotypes of people in Japan are better understood, there will be other benefits too. Obtaining these data can provide valuable information as to likely genetic components in health and disease. 'There is a complex and intricate relationship between the exact genetics of a person and their likelihood of developing certain diseases,' says Saitou. 'Cancers are perhaps the most obvious example, deriving from mutations in particular

suspected that the large parts of the human genome that are non-coding have a key role in this process.' These are also the regions of the genome that Saitou is interested to carry out his evolutionary studies as he is convinced that they provide the region of key changes and the origins of vast genetic diversity.

Sequencing genomes is merely the first step towards understanding the genetic information. In order to derive anything of use from the sequencing process, sophisticated analyses need to be conducted. Saitou and his team are also leaders in these types of analyses. 'Indeed, I developed a novel method, called 'Neighbor-Joining method', of extracting phylogenetic information during my PhD that is still in use today,' he enthuses. 'Our research on new methods for molecular evolutionary studies will mostly impact on evolutionary biologists,' he observes. However, he comments that as the Neighbor-Joining method (Saitou and Nei, 1987) is even now widely used, not only for biologists, but also for many people who are interested in phylogenetic trees, their future new methods may also have a much broader impact. ●

Project Insights

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