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Title: Phylogeny, human evolution, and CNSs: three main areas I studied for almost 45 years of my research

## Abstract

When I was sophomore in the University of Tokyo, 19 years old in 1976, I came to know the neutral theory of evolution by reading a Japanese review article written by Dr. Kimura Motoo (ref. 1). I immediately fell in love with this theory, and started to learn population genetics theory and molecular evolution. When I was senior at Department of Biology, majoring in physical anthropology, I decided to study genetical anthropology under Professor Omoto Keiichi. I carefully read one paper on molecular phylogeny written by Cavalli-Sforza and Edwards in 1967 (ref. 2). I was asked to explain this paper by Omoto laboratory members including Dr. Horai Satoshi, who later joined NIG. This experience gave me a great hint when I developed the neighbor-joining method (ref. 3).

In my master course, I estimated the age of mutants found in Philippine Negrito populations by Professor Omoto's group, applying a branching process. This was my master thesis, but my first academic paper was estimation of migration pattern in Japan using surname data collected through telephone books. This paper, written in Japanese, was published in 1983 (ref. 4), when I was in Houston, Texas. After visiting Negrito villages in the Philippines from December 1981 to January 1982, I joined Professor Masatoshi Nei's Laboratory in University of Texas, Houston in the summer of 1982. Nei Laboratory was a stronghold of the neutral theory at that time. Drs. Wen-Hsiung Li and Ranajit Chakaraborty were faculty members, Drs. Gojobori Takashi and Chung-I Wu were postdoc, and Drs. Tajima Fumio and Dan Graur were graduate students.

During four years in Houston, I worked pretty hard, and my Ph.D thesis consisted of three chapters including proposal of the neighbor-joining method. I also analyzed influenza A virus gene sequence data, and published two papers, but did not combine these with my Ph.D. thesis. I returned to Japan in fall of 1986, and did two years of JSPS postdoctoral fellow. During that period, I visited ethnic minorities in Hainan Island, China with Professor Omoto. I then became an assistant professor at Department of Anthropology, Faculty of Science, the University of Tokyo in 1989. I visited indigenous peoples in Taiwan with Dr. Horai Satoshi in 1990 and 1991.

Professor Gojobori Takashi, who became head of DDBJ at NIG at that time, asked me to join DDBJ. I was very pleased with this offer, and joined NIG as associate professor at Division of Evolutionary Genetics on January 16th, 1991. Therefore, I have been at NIG for slightly more than 31 years, though I worked for DDBJ until 2008. During this period, I published 233 papers and books. Among them, 23 are single-authored ones (mainly review articles) and 9 are first-authored ones. I am corresponding author of 45 papers that were first-authored by my former students and postdocs.

Papers that were mainly produced by SAITOU Lab members are very heterogenous. For example, Satoshi Oota, my first Ph.D. student, estimated the phylogeny of muscle tissues (ref. 5). This work was mentioned by Nick Lane's book (ref. 6) for general audience. One of my nephews who went to law school read its Japanese translation, and he was surprised by finding my name in that book. Though this paper was cited only 93 times according to Google Scholar, I am happy with this episode.

When I moved to NIG, I just started to analyze human ABO blood group gene sequences. I contacted Dr. Fumiichiro Yamamoto, who determined the nucleotide sequences of human ABO genes for collaboration. I suggested him to determine non-human ABO blood group sequences, and he did. Therefore, when Takashi Kitano, my second Ph.D student, joined my laboratory in 1996, I suggested him to study orthologs of human Rh blood group genes and its paralogous genes. We

collected bone marrow samples from mice, rat, and crab-eating macaque, and determined Rh and Rh50 gene sequences (ref. 7).

In 2000, determination of the draft human genome sequences was announced. Area of molecular evolution should also move to evolutionary genomics. I thus started Ape Genome Project, nicknamed Silver, for atomic symbol of silver is Ag. With the help of Dr. Fujiyama Asao, Dr. Kim Chun-Gong produced gorilla fosmid library (ref. 8). My laboratory was also involved in the international chimpanzee chromosome 22 sequencing project headed by Dr. Sakaki Yoshiyuki.

However, I was also interested in gene hunting, and focused on ear wax gene. Ear wax has a long history of research in Japan. Dr. Takahashi Aya, who just received Ph.D. in University of Chicago under Professor Chung-I Wu, joined my lab as a post-doc in 2000, and I suggested her to hunt for ear wax gene. In one day in 2002, I found a surprising news in a Japanese weekly magazine; Nagasaki University group discovered the ear wax gene. I was shocked, but found the corresponding paper and was relieved to know that they only narrowed down the chromosome region for the ear wax gene. I quickly contacted Professor Niikawa Norio at Nagasaki University Medical School, and my laboratory joined the ear-wax hunting team. Eventually, four years later, ABCC11 was found to be the gene for ear wax (ref. 9). My former student Ishibashi Minaka, as well as Takahashi Aya and myself, were coauthors of this paper.

When Takahashi (now Ueda) Mahoko joined my lab as the 11th Ph.D. student in 2005, I suggested her to study CNSs (Conserved Noncoding Sequences) among primates and rodents. Matsunami Masatoshi, my 12th Ph.D. student, also studied CNSs, but he first focused on Hox gene clusters, and his paper (ref. 10) was the first CNS related paper published from Saitou Laboratory. Later, three students from Nigeria (Isaac Babarinde), Sri Lanka (Nilmini Hettiarachchi), and Iran (Mahmoudi Saber Morteza), as well as Inoue Jun, who constructed dbCNS (<http://yamasati.nig.ac.jp/dbcns/>), also studied CNS evolution.

Meanwhile, Timothy A. Jinam joined my laboratory as Ph.D. student in 2008. He already had experience of analyzing genome-wide SNP data of modern human populations in Malaysia. I thus suggested him to study similar data of Japanese populations. He has been very productive, and after doing postdoc at Division of Human Genetics, NIG, he became assistant professor of my laboratory after Dr. Sumiyama Kenta moved out to Riken Center for Biosystems Dynamics Research. Tim is an important member of our “Yaponesia Genome Project” (<http://www.yaponesia.jp>).

Kanzawa Hideaki became Ph.D student of my laboratory in 2009, and he wanted to study ancient DNA. I managed to find some grant from Indus Project at Research institute for Humanity and Nature to set up a primitive aDNA working space in my laboratory, and he eventually obtained partial genome sequence of Jomon people, and we published a paper in 2016 (ref. 11).

In 2020 A.D. (or in my year, year 0020), I started a new online journal “iDarwin” (<http://idarwin.org>) on the birthday of Charles Darwin (ref. 12). At this moment, not many articles are published in this journal, however, I do hope that this journal will become an important asset for evolutionary studies.

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English seminar: Yes