Abstract

Our Unit started in May 2020. We build on previous work where we sequenced the genomes of Denisovans and Neandertals, hominin groups that diverged from modern humans about half a million years ago. Our goal is to identify genetic changes that resulted in phenotypes that differed between modern and extinct hominins.

1. Staff

- Xiangchun Ju, Postdoc
- Shin-Yu Lee, Postdoc
- Chika Azama, Technician
- Limin Chen, Technician
- Chie Narai, Research Unit Administrator

Visiting Researcher

- Hugo Zeverg, Visiting researcher (Karolinska Institutet)
- Mateja Hajdinjak, Visiting Researcher (Max Planck Institute)

2. Collaborations

2.1. Prof. Hugo Zeberg, Karolinska Institutet, Stockholm, Sweden

- Effects of archaic genetic variants in present-day populations.

2.2. Prof. Bernd Kuhn, OIST

- Effects of human-specific genetic changes.

2.3. Prof. Izumi Fukunaga, OIST

- Effects of human-specific changes in the gene ADSL.

2.4. Prof. Kazumasa Tanaka, OIST

- Effects of human-specific changes in the gene ADSL.

2.5. Prof. Wieland Huttner, Max Planck Institute for Cell Biology and Genetics, Dresden, Germany

- Effects of human-specific changes in genes involved in chromosomal segregation.

2.6. Prof. Ryosuke Kimura, University of the Ryukyus,

- Population history of the Ryukyus.

2.7. Prof. Ken-ichi Shinoda, National Museum of Nature and Science, Tokyo

- Population history of Japan.

2.8. Tohoku Medical Megabank Organization, Tohoku University

Archaic genetic contributions to the Japanese population.

- Prof. Fuji Nagami, Project Director
- Prof. Nobuo Fuse, Assistant Prof. Makiko Taira
- Prof. Kengo Kinoshita, Assistant Prof. Shu Tadaka

3. Activities and Findings

3.1: Genetic changes specific to modern humans

We study genetic changes unique to humans as well as archaic genetic contributions to present-day populations. We also develop methods to introduce single nucleotide changes into mammalian genomes.

Adenylosuccinate lyase (ADSL). We have showed that an amino acid change unique to modern humans in the enzyme adenylosuccinate lyase (ASDSL) reduces de novo purine biosynthesis (Stepanova et al., 2021). We have introduced this change into mice and are perform more detailed analyses of the metabolic effects as well as effects on the behavior of the mice. We also analyze the effects on muscle function and performance. In parallel, we study an amino acid change unique to Neandertals in the enzyme adenosine monophosphate deaminase (AMPD1), involved in purine recycling and in skeletal muscle.

Mitosis during brain development. We examine six such amino acid substitutions in three proteins (KNL1, KIF18A, SPAG5) which have roles in kinetochore function and chromosome segregation. We have introduced these modern human-specific substitutions in mice and the ancestral substitutions into human brain organoids. Last year, we found that they prolong mitotic metaphase and reduce errors in chromosome segregation in neuronal progenitors (Mora-Bermudez et al., 2022). Currently, the behavior of mice carrying some of these changes is investigated.

3.2: Genome editing methods

We develop improved methods for the introduction of single nucleotide changes in the human genome. We have developed an approach where diagnostic substitution in the donor molecules used in editing are used to ensure that unintended deletions have not affected the editing site (Lackner et al., 2023).

We have also developed HDRobust, a method that, by the combined transient inhibition of nonhomologous end joining and microhomology-mediated end joining, allow the efficient introduction of point mutations in populations of human cells with few unintended side effects (Riesenberg et al., 2023).

3.3: Population history of the Ryukyus and Japan.

We have initiated collaborations with the University of Ryukyu, the National Museum of Nature and Science, and Tohoku University to study the early peopling of the Ryukyu Islands and the composition of the gene pool of Japan with respect genetic contributions from Neandertals and Denisovans.

4. Publications

4.1 Journals

Lackner, M., Helmbrecht, N., Pääbo, S., & Riesenberg, S. (2023). Detection of unintended on-target effects in CRISPR genome editing by DNA donors carrying diagnostic substitutions. Nucleic Acids Research, 51(5): gkac1254.

Ågren, R., Patil, S., Zhou, X., Sahlholm, K., Pääbo, S., & Zeberg, H. (2023). Major genetic risk factors for Dupuytren's disease are inherited from Neandertals. Molecular Biology and Evolution, 40(6): msad130.

Riesenberg, S., Kanis, P., Macak, D., Wollny, D., Düsterhöft, D., Kowalewski, J., Helmbrecht, N., Maricic, T., & Pääbo, S. (2023). Efficient high-precision homology-directed repair-dependent genome editing by HDRobust. Nature Methods, 20, 1388-1399.

Zeberg, H., Jakobsson, M., & Pääbo, S. (2024). [Review] The genetic changes that shaped Neandertals, Denisovans, and modern humans. Cell, 187, 1047-1058.

Xing, L., Gkini, V., Nieminen, A. I., Zhou, H.-C., Aquilino, M., Naumann, R., Reppe, K., Tanaka, K., Carmeliet, P., Heikinheimo, O., Pääbo, S., Huttner, W. B., & Namba, T. (2024). Functional synergy of a human-specific and an ape-specific metabolic regulator in human neocortex development. Nature Communications, 15: 3468.

5. Intellectual Property Rights and Other Specific Achievements

Nothing to report.

6. Meetings and Events

6.1 Public Lecture

Nobel Prize Season Special Public Lecture by Prof. Svante Pääbo (2022 Nobel Prize Laureate in Physiology or Medicine) “Denisovans and Neanderthals: How They Live on in Us”

- 7th October, 2023, 14:00-16:00, at OIST Auditorium
- 9th October, 2023, 14:00-16:00, at Aim Universe Tedako Hall

7. Other

7.1 Honors

- Doctor of Science honoris causa, American Museum of Natural History, New York, USA.
- Foreign Member of the Chinese Academy of Sciences, Beijing.
- Alumnus of the Year, Uppsala University, Sweden.