

TITLE OF REPORT : Unique structure and pleiotropic disease associations of a gene

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My JSPS BRIDGE Fellowship visit to Prof. Katsushi Tokunaga at University of Tokyo's Department of Human Genetics took place from July 31st to August 13th, 2018, and it was highly successful. Although it was unusually hot and humid in Japan during this period, to the extent that Japanese newspapers were reporting heat-stroke-associated deaths daily, and I myself suffered heat stroke right after my arrival, I was able to recover quickly and manage to work productively with Prof. Tokunaga and Drs. Kawai and Yanai in his team, thanks to their support and JSPS.

Our research plan was to study a gene which I had found to possess multiple peculiar characteristics. Specifically, prior to the visit, I had noticed an unusual genomic structure and its human-specific pattern of the gene, examined its haplotypes across six different world populations, finding that they are quite diverse across populations, and also discovered associations of the haplotypes with the risk of an autoimmune disease, utilizing the data Prof. Tokunaga and his colleague provided to me following my previous JSPS visit to his laboratory. I was quite excited to be able to discuss these with Prof. Tokunaga who has deep knowledge of genetics and human diseases.

During the two-week period of my visit this time, following Prof. Tokunaga's suggestion to examine the disease risk association more broadly in an European population, I examined the haplotypes' associations with many disease phenotypes in the cohort of childhood cancer survivors we follow up at St. Jude Children's Research Hospital (St. Jude Life Time Cohort Study), adjusting for relevant risk factors of each disease, and found over 15 diseases whose risks are associated with the haplotypes of the gene. This was quite surprising and exciting to us: not only this gene has the special structure that is somewhat inconsistent with the current understanding of human genome, it has so-called "pleiotropic" associations with many diseases including cancer and cardiovascular diseases. We are currently following up this finding with multiple approaches and begin to understand the biology underlying these associations. This includes an analysis of additional data from the UK Biobank database that has ~ 500,000 UK general-population individuals' genomic and disease data and trying to confirm our findings firmly in the largest general population data of its

kind, as well as another childhood cancer survivor database.

In addition, following the suggestion of Dr. Yanai and Prof. Tokunaga, I met with Dr. Kawai who has strong expertise in evolutionary genetics, to follow up the finding of the human-specific pattern of this gene. Dr. Kawai explained to me that my reasoning of the human-specificity is not sound and proposed and conducted an alternative analytic approach to compare the human haplotypes I identified with those of archaic human (Neanderthals and Denisovans) and apes (chimpanzees and gorillas). My team would not have been able to conduct such an analysis easily, but Dr. Kawai was able to perform it and obtain the result swiftly. His analysis result was quite striking: it showed that these haplotypes are indeed indicating a human-specific pattern and has important evolutionary implications. We are following up this exciting finding from multiple directions.

In summary, our research progressed exceptionally well during my JSPS visit and it accelerated and elevated our collaborative work to the next stage. We intend to publish these finding after the analysis of the UK database in a leading journal of biomedical sciences.

While I almost entirely focused on the above project during the two-week visit with Prof. Tokunaga and his team, I had an opportunity to give a seminar at University of Tokyo with a title of “New statistical approaches to genome-wide association analysis” on August 2nd.

I would like to thank JSPS for supporting and providing me with this exceptional opportunity to collaborate with leading Japanese scientists.

Photo with Prof. Tokunaga (center) and Dr. Kawai (left) during discussion.

