



To the Press

World's Largest Whole Genome Sequencing of Renal Cancer: mutational signature linked to an unknown exposure discovered in 70% of Japanese samples

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National Cancer Center

The Institute of Medical Science, The University of Tokyo

Cancer Grand Challenges

Highlights

- An international study involving 11 countries including Japan conducted whole genome sequencing on 962 renal cell carcinoma case samples, the largest dataset of its kind.
- The analysis revealed a mutational signature in 70% of Japanese renal cell carcinoma samples, which is rarely seen in other countries.
- The signature is caused by exposure to an unknown mutagen, work is ongoing to identify the nature and source of the mutagen, and whether mutations linked to exposure are enough to cause cancer.
- The study also looked into known risk factors associated with renal cell carcinoma, finding smoking directly damaged genes, whereas other risk factors promoted development of renal cell carcinoma by other means.

Summary

Tatsuhiko Shibata's team at the National Cancer Center Research Institute took part in an international collaborative study, analysing 962 clear cell renal cell carcinoma samples from 11 countries, their findings were published in *Nature* on 1 May 2024. The project was part of Cancer Grand Challenges team Mutographs, in partnership with the Wellcome Sanger Institute and International Agency for Research on Cancer (IARC). The Mutographs team is funded by Cancer Research UK, through Cancer Grand Challenges, a £400m+ global funding initiative co-founded by Cancer Research UK and the National Cancer Institute in the US. Dr Shibata is Chief of the Division of Cancer Genomics at the National Cancer Center Research Institute, doubly appointed as Professor of the Laboratory of Molecular Medicine, the Human Genome Center, the Institute of

Medical Science of the University of Tokyo.

Results demonstrated that more than 70 percent of Japanese renal cell carcinoma samples were related to an unknown mutational signature very rarely observed in other countries. Of the known risk factors associated with renal cell carcinoma, obesity, high blood pressure and diabetes promoted cancer via non-mutagenic mechanisms, whilst smoking seemed to directly trigger mutations.

Further studies will be conducted, to elucidate the unknown mutagenic factors, and whether mutations linked to exposure are enough to cause cancer, towards developing prevention strategies for renal cell carcinoma. Whole genome sequencing analyses of tumour samples from various regions are anticipated to shed light onto the relationship of incidence variations to ethnicity and lifestyle factors, towards forming a global prevention strategy. The renal cell carcinoma study follows the team's previous esophageal squamous cell cancer study.

The study is funded by Cancer Research UK, through the Cancer Grand Challenges initiative, and Japan Agency for Medical Research and Development (AMED). The data will be made available to researchers through the International Cancer Genome Consortium-Accelerating Research in Genomic Oncology (ICGC-ARGO).

Prospects

This epidemiological study paired with whole genome sequencing was conducted with international partners, following the esophageal squamous cell cancer study. It demonstrates the effectiveness of whole genome sequencing, in unraveling the molecular mechanisms of carcinogenesis in each country. Of significance is the mutational signature specific to Japanese cases. Causative agents are still unclear, whole genome analysis of samples from multiple regions within Japan is planned with several institutions. The identification of causative substances, and their mechanisms, may lead to developing new prevention and treatments for clear cell renal cell carcinoma. A whole genome sequencing project is ongoing at a national level, with funds from the Japan Agency for Medical Research and Development (AMED), aggregating whole genome sequencing data of many cancer types. Further analysis of mutational signatures is anticipated to unravel the carcinogenic molecular mechanisms in Japan, leading the way to developing prevention methods.

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