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Global whole genome sequencing research on esophageal cancers reveals carcinogenic mechanisms specific to Japan

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National Cancer Center, Japan

Summary

- **Scientists from eight countries joined forces in whole genome sequencing research to establish evidence to underpin the prevention of esophageal cancers.**
- **The study demonstrated an increase in the characteristic mutation pattern due to alcohol consumption from Japanese patients. Further research is expected to lead towards better prevention methods.**
- **This work predates others in manifesting the power of combining whole-genome sequencing with epidemiological research. Large whole-genome sequencing projects recently launched in Japan are anticipated to identify the causes of various cancers, driving cancer prevention further, building on these findings.**

The National Cancer Center (president: Hitoshi NAKAGAMA) has participated in the Cancer Grand Challenge ‘Mutographs’ project, led from Wellcome Sanger Institute, in collaboration with the WHO International Agency for Research on Cancer (IARC). The Division of Cancer Genomics, led by Tatsuhiro Shibata at the National Cancer Centre Research Institute, joined a global effort spanning eight countries, with China, Iran, UK, Kenya, Tanzania, Malawi, and Brazil on esophageal squamous cell carcinoma, suffered by over 90 percent of Japanese patients. Five hundred fifty-two cases in total were analyzed with whole-genome sequencing and made available to the world.

The global effort elucidated the etiology of esophageal squamous cell carcinoma in various regions with diverse ethnicities and lifestyles through whole-genome sequencing. With an objective for developing prevention methods, it is the very first global joint study combining epidemiology and genomics.

The study revealed that lifestyle factors such as alcohol consumption, and germline variations related to alcohol metabolizing enzymes (ALDH2) and BRCA, are associated with the mutagenesis in esophageal cancer by analyzing the unique pattern of DNA mutations of tumors. In particular, the SBS16 mutational signature, related to alcohol

consumption, was noticeably prevalent in Japan and Brazil. Patients with a history of alcohol consumption showed the TP53 mutation as a result of SBS16.

The research was funded by Japan Agency for Medical Research and Development (AMED); the findings were reported in an article on *Nature Genetics* on 18 October 2021. The dataset will be registered on the International Cancer Genome Consortium Accelerating Research in Genomic Oncology (ICGC-ARGO) and accessible to all scientists.

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Publication

Authors	Sarah Moody, Sergey Senkin, S M Ashiqul Islam, Jingwei Wang, Dariush Nasrollahzadeh, Ricardo Cortez Cardoso Penha, Stephen Fitzgerald, Erik N Bergstrom, Joshua Atkins, Yudou He, Azhar Khandekar, Karl Smith-Byrne, Christine Carreira, Valerie Gaborieau, Calli Latimer, Emily Thomas, Irina Abnizova, Pauline E Bucciarelli, David Jones, Jon W Teague, Behnoush Abedi-Ardekani, Stefano Serra, Jean-Yves Scoazec, Hiva Saffar, Farid Azmoudeh-Ardelan, Masoud Sotoudeh, Arash Nikmanesh, Michael Eden,Paul Richman, Lia S Campos, Rebecca C Fitzgerald, Luis Felipe Ribeiro, Charles Dzamalala, Blandina Theophil Mmbaga, Tatsuhiro Shibata, Diana Menya, Alisa M Goldstein, Nan Hu, Reza Malekzadeh, Abdolreza Fazel, Valerie McCormack, James McKay, Sandra Perdomo, Ghislaine Scelo, Estelle Chanudet, Laura Humphreys, Ludmil B Alexandrov, Paul Brennan, Michael R Stratton
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