Unveiling the Landscape of Genomic Alterations in Adult T-Cell Leukemia/Lymphoma

A Demonstration of the Potential of Whole-Genome Sequencing Technology

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National Cancer Center Japan
Keio University School of Medicine
University of Miyazaki
Kyoto University
Japan Agency for Medical Research and Development

A joint research group led by Dr. Keisuke Kataoka at Keio University/National Cancer Center Research Institute Japan has completed a large-scale whole-genome sequencing study of adult T-cell leukemia/lymphoma (ATL). This research was conducted together with Professor Kazuya Shimoda at University of Miyazaki and Professor Seishi Ogawa at Kyoto University. The results of this study were published in the online edition of the American journal *Blood* on October 25, 2021.

Recent cancer genome studies have broadened the catalog of driver alterations and highlighted the promise of genome-driven oncology care. However, such large-scale genetic studies, especially those incorporating whole-genome sequencing (WGS), have not been adequately performed for rare cancers, hindering novel driver discovery and refinement of their treatment strategies. In this study, we present a high-depth (95.5× depth) WGS analysis of 150 paired tumor-normal samples with human T-cell leukemia virus type-1 (HTLV-1)-induced adult T-cell leukemia/lymphoma (ATL) to uncover the overall picture of genetic alterations in ATL. Our findings are summarized as follows:

1. Combining the analyses for coding and non-coding mutations, structural variations (SVs), and copy number alterations, we discovered 56 recurrently altered driver genes, including 11 novel ones, in ATL. Clustering of patients using these driver genes identified two molecular subgroups with distinct genetic and clinical characteristics.

2. We identified frequent (33%) loss-of-function mutations and deletions preferentially targeting the long isoform of *CIC*, a tumor suppressor frequently mutated in several cancer types. Notably, the long isoform-specific exons were recently discovered but previously overlooked by whole-exome sequencing studies. In addition, through mouse phenotyping, we found that long but not short isoform-specific inactivation of *Cic* selectively increases Foxp3-positive T cells in vivo, providing novel insights into T-cell biology.

3. We have elaborated the analytical approach for identifying gain-of-function SVs by calculating breakpoint frequency per intron. With this approach, we identified recurrent 3′-truncations of *REL* (13%), encoding an NF-κB subunit c-Rel. These truncations induce transcriptional upregulation and generate gain-of-function forms of c-Rel protein. More importantly, *REL* truncations are also common in diffuse large B-cell lymphoma (12% in germinal center B-cell-like and 6% in unclassifiable type). These findings not only highlight shared mechanisms driving T- and B-cell lymphomagenesis but also have implications for genome-wide cancer driver discovery.

4. Our study derives insights into the etiology of mutations and SVs, associating immune-related molecules and *EP300* with an increased burden of various alterations. We also comprehensively characterize the non-coding genome of ATL, identifying recurrent mutations in non-coding elements (particularly splice sites) of several driver genes.

The results of this study manifest the potential of whole-genome sequencing analysis and represent a significant advance in understanding the genetic and biological basis of ATL pathogenesis with clinical implications.

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For further information, please refer to the Japanese version of this press release (PDF file).

Details of the original paper

Authors Yasunori Kogure, Takuro Kameda, Junji Koya, Makoto Yoshimitsu, Kisato Nosaka, Jun-ichirou Yasunaga, Yoshitaka Imaizumi, Mizuki Watanabe, Yuki Saito, Yuta Ito, Marni B. McClure, Mariko Tabata, Sumito Shingaki, Kota Yoshifuji, Kenichi Chiba, Ai Okada, Nobuyuki Kakiuchi, Yasuhito Nannya, Ayako Kamiunten, Yuki Tahira, Keiichi Akizuki, Masaaki Sekine, Kotaro Shide, Tomonori Hidaka, Yoko Kubuki, Akira Kitanaka, Michihiro Hidaka, Nobuaki Nakano, Atae Utsunomiya, R. Alejandro Sica, Ana Acuna-Villaorduna, Murali Janakiram, Urvi Shah, Juan Carlos Ramos, Tatsuhiro Shibata, Kengo Takeuchi, Akifumi Takaori-Kondo, Yasushi Miyazaki, Masao Matsuoka, Kenji Ishitsuka, Yuichi Shiraishi, Satoru Miyano, Seishi Ogawa, B. Hilda Ye, Kazuya Shimoda, and Keisuke Kataoka

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● Research & Development Inquiries

Division of Molecular Oncology, National Cancer Center Research Institute Japan
Yasunori Kogure, M.D., Ph.D.
5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
Telephone: +81-3-3542-2511
E-mail: ykogure@ncc.go.jp

Keio University School of Medicine, Department of Hematology
Professor Keisuke Kataoka, M.D., Ph.D.
Telephone: +81-3-5363-3785
E-mail: kekataok@keio.jp

● Media Inquiries

National Cancer Center Japan
Office of Public Relations, Strategic Planning Bureau
5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
E-mail: ncc-admin@ncc.go.jp

Keio University
Office of General Affairs, Keio University Shinanomachi Campus
35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan
E-mail: med-koho@adst.keio.ac.jp

University of Miyazaki
General Affairs Department, University of Miyazaki
1-1 Gakuen Kibanadai-nishi, Miyazaki 889-2192
E-mail: kouhou@of.miyazaki-u.ac.jp

Kyoto University
Global Communications Office
Yoshidahonmachi, Sakyo-ku, Kyoto 606-8317
E-mail: comms@mail2.adm.kyoto-u.ac.jp

- AMED Inquiries

Japan Agency for Medical Research and Development
Practical Research for Innovative Cancer Control, Division of Basic Medical Research, Department of Basic Medical Research
1-7-1 Otemachi, Chiyoda-ku, Tokyo 100-0004
E-mail: cancer@amed.go.jp