IMSUT Hospital

Department of Applied Genomics
ゲノム診療科
Department of Clinical Genomics
ゲノム診療部

Professor Yoichi Furukawa, M.D., Ph.D.

教 授 博士(医学) 古 川 洋 一

Our department has been working on the application of human genome information in clinics. As clinical services in IMSUT Hospital, we provide genetic counseling, genetic tests for human diseases, and a surveillance program for patients with hereditary colorectal cancer. In addition, we have been carrying out two research projects; 1) determination of genetic alterations in human tumors, and elucidation of the mechanisms underlying their development, and 2) clinical sequence for the implementation of genomic medicine.

1. Genetic test of human neoplasms

Yoichi Furukawa

As a part of clinical service, we have performed genetic analysis of human neoplasms including colorectal cancer. A total of 21 cases were analyzed by WGS in 2024. The results were utilized for the precise classification of neoplasms, evaluation of disease status, selection of therapeutic drugs, and evaluation of the response to treatment.

2. Genetic counseling and related activities

Yoichi Furukawa, Takashi Okada, Yataro Daigo, Koichiro Yuji, Reiko Sada, Mitsuko Nakazawa, Miho Iigaya[1], Yoshinari Miyamoto[2], Masae Ono[3], Mayumi Tamari[4], Shiro Ikegawa[5], Hidewaki Nakagawa[6], Natsuko Watanabe[7], Ai Yoshihara[7], Toru Akiyama[8]: [1]Kitasato University, [2]National Center for Global Health and Medicine, [3]Yotsuba Mirai Clinic, [4]Jikei Medical University, [5]National Rehabilitation Center for Children with Disabilities, [6]Center for Integrative Medical Sciences, RIKEN, [7]Ito Hospital, [8]Jichi Medical University.

In IMSUT hospital, we provided genetic counseling and genetic tests to clients who visited our counseling clinic. In 2024, we had a total of 40 counseling cases with various hereditary diseases such as muscular dystrophy, Huntington's disease, Ehlers-Danlos syndrome, hereditary breast and ovarian cancer, and Lynch syndrome. In the counseling, we provided appropriate information about the diseases to the clients and took their psychological care in collaboration with a clinical psychologist. Genetic testing was performed in cases with informed consent after thoughtful discussion about its merit and demerit.

Systematic surveillance programs are provided for the patients susceptible for hereditary tumors.

3. Identification of pathogenic germline variants in patients with biliary tract cancer: insights from 799 Japanese cases

Kiyoko Takane[1], Kiyoshi Yamaguchi[1], Tsuneo Ikenoue, Yoichi Furukawa

[1]Division of Clinical Genome Research, Advanced

Clinical Research Center

Biliary tract cancer (BTC) is a group of malignancies that include intrahepatic cholangiocarcinoma (ICC), extrahepatic cholangiocarcinoma (ECC), gallbladder carcinoma (GBC), and ampulla of vater carcinoma (AVC). Although BTC is relatively rare, it is a highly aggressive disease with a poor prognosis, largely due to its frequent diagnosis at late-stages and limited treatment options. The incidence of BTC is particularly high in East Asia and South America, likely due to a combination of environmental, lifestyle, and genetic factors. Despite advances in diagnostic technologies and treatment modalities, the overall survival rates for BTC patients remain dismal compared to other gastrointestinal cancers.

Recent studies suggest that germline variants in homologous recombination repair (HRR) genes may contribute to BTC development. Therefore, in this study, we analyzed 799 Japanese BTC cases from Biobank Japan using amplicon sequencing, focusing on key HRR genes including *BRCA1*, *BRCA2*, *PALB2*, *BARD1*, *BRIP1*, *RAD51C*, *RAD51D*, *RAD50*, *FANCM*, *ATM*, *CHEK2*, and *NBN*. Germline variants were assessed using ClinVar, gnomAD, and TogoVar databases, and consequently pathogenic variants were identified in 30 cases. The variants included those in *BRCA1* (8 cases), *BRCA2* (5 cases), *PALB2* (6 cases), *BRIP1* (2 cases), *RAD51D* (2 cases), *RAD50* (1 case), *FANCM* (1 case), *ATM* (4 cases), and *CHEK2* (1 case). As we expected, a significant correlation between pathogenic HRR variants and family history of cancer was observed. This finding underscores the potential importance of hereditary cancer predisposition in BTC and highlights the need for genetic screening in patients with family history of malignancies. Such efforts may allow earlier detection of BTC and more personalized therapeutic interventions.

4. Clinical sequencing for the implementation of genomic medicine

Kiyoko Takane, Kiyoshi Yamaguchi, Yoichi Furukawa, Eigo Shimizu[1], Rika Kasajima[1], Kotoe Katayama[1], Seiya Imoto[1], Tetsuo Shibuya[2], Kazuaki Yokoyama[3], Yasuhito Nanya[3], Koichiro Yuji[4], Rui Yamaguchi[5], Satoru Miyano[6]: [1]Division of Health Medical Intelligence, [2]Division of Medical Data Informatics, Human Genome Center, [3]Department of Hematology/Oncology, [4]Project Division of International Advanced Medical Research, Advanced Clinical Research Center, IMSUT, [5]Division of Cancer Systems Biology, Aichi Cancer Center Research Institute, [6]M&D Data Science Center, Institute of Integrated Reseach, Institute of Science ToKyo

The application of Next-Generation Sequencing (NGS) technology in clinical medicine has revolutionized molecular diagnostics by enabling multiple gene testing, or analysis of the entire exon or whole genome with a limited amount of DNA. In collaboration with Human Genome Center and Advanced Clinical Research Center, we have been working on the genetic diagnosis of patients with suspected hereditary cancer predisposition, and the implementation of precision medicine for patients with rare or intractable cancer.

We have applied NGS technology for molecular diagnostics of hereditary colon cancer syndromes such as familial adenomatous polyposis (FAP), Lynch syndrome (LS), and polymerase proofreading-associated polyposis (PPAP). In addition to short read-sequencing, we took advantage of MinION, a long-read sequencer of Oxford nanopore platform, for the detection of pathogenic structural variants (SVs) because not only single nucleotide variants (SNVs) and short insertions and deletions (indels) but also structural variations (SVs) are responsible for the predisposition of hereditary cancer. Utilizing MinION, we have successfully identified the breakpoint of a pathogenic SV that could not be determined by short-read sequencing technology.

We have been also working on the implementation of genomic data in clinics. Patients with various types of cancer who gave written informed consent for genetic analysis were enrolled in this study. Genetic alterations in their tumors were identified using NGS, and the data were subsequently analyzed by QIAGEN Clinical Insights (QCI). Actionable variants were reviewed and discussed in a tumor board to determine recommended therapeutic options. This multidisciplinary board comprised physicians, medical oncologists, genetic counselors, geneticists, bioinformaticians, and ethics experts, and convened online every two weeks.

Publications

1. Noguchi, R., Yamaguchi, K., Yano, H., Gohda, Y., Kiyomatsu, T., Ota, Y., Igari, T., Takahashi, N., Ohsugi, T., Takane, K., Ikenoue, T., Niida, A., Shimizu, E., Yamaguchi, R., Miyano, S., Imoto, S. and Furukawa, Y. Cell of origin and expression profiles of pseudomyxoma peritonei derived from the appendix. Pathol Res Pract. 2024 in press
2. Takane, K., Cai, T., Noguchi, R., Gohda, Y., Ikenoue, T., Yamaguchi, K., Ota, Y., Kiyomatsu, T., Yano, H., Fukuyo, M., Seki, M., Bahityar, R., Kaneda, A. and Furukawa, Y. Genome-wide analysis of DNA methylation in pseudomyxoma peritonei originated from appendiceal neoplasms. Oncology. 102(8):720-731, 2024.