Human Genome Center

Division of Health Medical Intelligence
健康医療インテリジェンス分野

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Laboratory of Sequence Analysis
シークエンスデータ情報処理分野

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Our mission is to realize genomic medicine based on the integrated data analysis of whole genomes of human and commensal microbiota by supercomputing. Development of computational data analysis methods including artificial intelligence for genomic, health, and medical big data is one of our main focuses. We promote integrative analysis of human whole genome, RNA and other omics data, commensal microbiota including bacteriome and virome, and health and medical-related big data. Furthermore, health medical intelligence aims at using the analysis results of such big data to create personalized health-medical action plan of individuals.

1. Whole Genome Sequencing and Genomic Medicine

a. Creating New Genomic Medicine by Integrating Human Whole Genome and Commensal Microbiota

Katayama K, Sato N, Shimizu E, Kasajima R, Yamaguchi K, Yokoyama K, Yadome M, Hyugaji T, Komura M, Yamamoto M, Saito A, Zhang Y-Z, Fujimoto K, Kobayashi M, Ogawa M, Takei T, Yasui H, Yuji K, Takane K, Ikenoue T, Robert B, Shibuya T, Hiroshima Y, Hasegawa T, Miyagi Y, Muto K, Goyama S, Shida D, Boku N, Kawabata K, Miyano S, Yamaguchi R, Uematsu S, Kumasaka N, Takahashi S, Nanya Y, Furukawa Y, Imoto S

Using state-of-the-art genome analysis and artificial intelligence, our mission is to implement "new genomic medicine" by integrating human genome information and human symbiotic microbial metagenome information.

In Japan, gene panel testing was covered by national health insurance from Jun 2019, however, it analyzed several hundreds of genes, which were known cancer-related genes. Since the gene panel has trivial limitation due to its focused genes, Japanese government considered to extend the gene panel to whole genome. However, it remains a question that whether the whole genome sequence information is

enough to realize precision medicine.

Although human genome has 20 thousand genes, intestinal microbiota has 20 million genes, and they work together with human genes for keeping homeostasis of our lives. In recent years, with the advancement of sequencing technology, we could have a whole figure of intestinal microbiota and found its dysbiosis leads to various diseases. We are proceeding a research for utilizing the information of intestinal microbiota (meta-genome) and human genome to create new genomic medicine in Society5.0. For this purpose, we need to establish an artificial intelligence to translate the information of human genome and meta-genome to clinical actions of physicians.

b. Establishment of Data Analysis Center in Action Plan for Whole Genome Analysis of Ministry of Health, Labour and Welfare

Katayama K, Shibuya T, Yamaguchi R, Kumasaka N, Matsuda K, Miyo K[1], Okamura H[2], Ota K[2], Shintani A[2], Shiraishi Y[3], Kohno T[3], Kato M[3], Okada Y[4], Fujimoto A[4], Kasai S[5], Imoto S: [1]National Center for Global Health and Medicine, [2]Osaka Metropolitan University, [3]National Cancer Center, Japan, [4]University of Tokyo School of Medicine, Japan, [5]Information-Technology Promotion Agency, Japan

Based on the Whole Genome Analysis Action Plan (Version 1) formulated on December 20, 2019 by the Ministry of Health, Labour and Welfare, the AMED project was launched in 2021 aiming at returning the result of WGS analysis to the patients as medical actions. This national project covers a wide range of intractable cancers, including gastrointestinal, hematological, pediatric, rare, gynecological, and respiratory cancers. A total of 9,900 patients will be subjected to whole genome sequencing analysis with depth of 30x for normal and 120x for tumor samples, and RNA sequencing will also be conducted.

Our team (PI: Prof. Seiya Imoto of IMSUT) is building the Analysis Data Center to collect and compile a database of genomic data and clinical information of these cancer patients. The mission of the Analysis Data Center is to construct a unified analysis pipeline for primary analysis of genomic data, to collect clinical information, to build a reporting system that can be used in expert panels, to build a secure data sharing system, and to build an analysis environment that can perform advanced secondary analysis in a hybrid computational environment of on-premises and cloud.

2. Metagenome Analysis of Intestinal Microbiota

a. Unveiling viral dark matter by whole metagenome analysis of bacteriome and virome

Fujimoto K, Kimura Y, Shimohigoshi M, Sato N, Zhang Y-Z, Katayama K, Satoh M, Sato S, Tremmel G, Uematsu M, Kawaguchi Y, Usui Y, Nakano Y, Hayashi T, Kashima K, Yuki Y, Yamaguchi K, Furukawa Y, Kakuta M, Akiyama Y[4], Yamaguchi R, Crowe SE[5], Ernst PB[6], Miyano S, Kiyono H, Imoto S, Uematsu S: [4]Department of Computer Science, Tokyo Institute of Technology, Japan, [5]Department of Medicine, University of California, San Diego, USA, [6]CU-UCSD Center for Mucosal Immunology, Allergy and Vaccines, University of California San Diego, USA.

The application of bacteriophages (phages) is proposed as a highly specific therapy for intestinal pathobiont elimination. However, the infectious associations between phages and bacteria in the human intestine, which is essential information for the development of phage therapies, have yet to be fully elucidated. Here, we report the intestinal viral microbiomes (viromes), together with bacterial microbiomes (bacteriomes), in 101 healthy Japanese individuals. Based on the genomic sequences of bacteriomes and viromes from the same fecal samples, the host bacteria-phage associations are illustrated for both temperate and virulent phages. To verify the usefulness of the comprehensive host bacteria-phage information, we screened Clostridioides difficile-specific phages and identified antibacterial enzymes whose activity is confirmed both in vitro and in vivo. These comprehensive metagenome analyses reveal not only host bacteria-phage associations in the human intestine but also provide vital information for the development of phage therapies against intestinal pathobionts.

b. Functional restoration of bacteriomes and viromes by fecal microbiota transplantation

Fujimoto K, Kimura Y, Allegretti JR[7], Yamamoto M, Zhang Y-Z, Katayama K, Tremmel G, Kawaguchi Y[8], Shimohigoshi M[8], Hayashi T[8], Uematsu M[8], Yamaguchi K, Furukawa Y, Akiyama Y[9], Yamaguchi R, Crowe SE[10], Ernst PB[10], Miyano S, Kiyono H, Imoto S, Uematsu S: [7]Brigham and Women's Hospital, Boston, Massachusetts, USA. [8]Osaka City University, [9]Department of Computer Science, Tokyo Institute of Technology, [10]University of California, San Diego.

Fecal microbiota transplantation (FMT) is an effective therapy for recurrent Clostridioides difficile infection (rCDI). However, the overall mechanisms underlying FMT success await comprehensive elucidation, and the safety of FMT has recently become a serious concern because of the occurrence of drug-resistant bacteremia transmitted by FMT. We investigated whether functional restoration of the bacteriomes and viromes by FMT could be an indicator of successful FMT. The human intestinal bacteriomes

and viromes from 9 patients with rCDI who had undergone successful FMT and their donors were analyzed. Prophage-based and CRISPR spacer-based host bacteria–phage associations in samples from recipients before and after FMT and in donor samples were examined. The gene functions of intestinal microorganisms affected by FMT were evaluated. Metagenomic sequencing of both the viromes and bacteriomes revealed that FMT does change the characteristics of intestinal bacteriomes and viromes in recipients after FMT compared with those before FMT. In particular, many Proteobacteria, the fecal abundance of which was high before FMT, were eliminated, and the proportion of Microviridae increased in recipients. Most temperate phages also behaved in parallel with the host bacteria that were altered by FMT. Furthermore, the identification of bacterial and viral gene functions before and after FMT revealed that some distinctive pathways, including fluorobenzoate degradation and secondary bile acid biosynthesis, were significantly represented.

3. Health Medical Data Science

a. Halcyon: an accurate basecaller exploiting an encoder-decoder model with monotonic attention

Konishi H, Yamaguchi R, Yamaguchi K, Furukawa Y, Imoto S

In recent years, nanopore sequencing technology has enabled inexpensive long-read sequencing, which promises reads longer than a few thousand bases. Such long-read sequences contribute to the precise detection of structural variations and accurate haplotype phasing. However, deciphering precise DNA sequences from noisy and complicated nanopore raw signals remains a crucial demand for downstream analyses based on higher-quality nanopore sequencing, although various basecallers have been introduced to date.

To address this need, we developed a novel basecaller, Halcyon, that incorporates neural-network techniques frequently used in the field of machine translation. Our model employs monotonic-attention mechanisms to learn semantic correspondences between nucleotides and signal levels without any pre-segmentation against input signals. We evaluated performance with a human whole-genome sequencing dataset and demonstrated that Halcyon outperformed existing third-party basecallers and achieved competitive performance against the latest Oxford Nanopore Technologies' basecallers.

b. Immunogenomic pan-cancer landscape reveals immune escape mechanisms and immunoediting histories

Mizuno S[11], Yamaguchi R, Hasegawa T, Hayashi S, Fujita M[12], Zhang F[13], Koh Y[14], Lee S-Y[15], Yoon S-S[14], Shimizu E, Komura M, Fujimoto A[12], Nagai M[16], Kato M[16], Liang H[17], Miyano S, Zhang Z[13], Nakagawa H[12], Imoto S: [11]Kyushu University, [12]Riken, [13]Peking University, [14]Seoul National University Hospital, [15]Samsung SDS, [16]National Cancer Center, Japan, [17]The University of Texas MD Anderson Cancer Center, USA.

Immune reactions in the tumor microenvironment are an important hallmark of cancer, and emerging immune therapies have been proven effective against several types of cancers. To investigate cancer genome-immune interactions and the role of immunoediting or immune escape mechanisms in cancer development, we analyzed 2834 whole genome and RNA sequencing datasets across 31 distinct tumor types with respect to key immunogenomic aspects and provided comprehensive immunogenomic profiles of pan-cancers. We found that selective copy number changes in immune-related genes may contribute to immune escape. Furthermore, we developed an index of the immunoediting history of each tumor sample based on the information of mutations in exonic regions and pseudogenes and evaluated the immunoediting history of each tumor. Our immuno-genomic analyses of pan-cancers have the potential to identify a subset of tumors with immunogenicity and diverse backgrounds or intrinsic pathways associated with their immune status and immunoediting history.

c. Enhancing breakpoint resolution with deep segmentation model: a general refinement method for read-depth based structural variant callers

Zhang Y-Z, Imoto S, Miyano S, Yamaguchi R:

Read-depths (RDs) are frequently used in identifying structural variants (SVs) from sequencing data. For existing RD-based SV callers, it is difficult for them to determine breakpoints in single-nucleotide resolution due to the noisiness of RD data and the bin-based calculation. In this paper, we propose to use the deep segmentation model UNet to learn base-wise RD patterns surrounding breakpoints of known SVs. We integrate model predictions with an RD-based SV caller to enhance breakpoints in single-nucleotide resolution. We show that UNet can be trained with a small amount of data and can be applied both in-sample and cross-sample. An enhancement pipeline named RDBKE significantly increases the number of SVs with more precise breakpoints on simulated and real data.

4. COVID-19

a. A nation-wide consortium to elucidate host genetics of COVID-19 pandemic in Japan

Japan COVID-19 Task Force

Identifying the host genetic factors underlying severe COVID-19 is an emerging challenge. Here we conducted a genome-wide association study (GWAS) involving 2,393 cases of COVID-19 in a cohort of Japanese individuals collected during the initial waves of the pandemic, with 3,289 unaffected controls. We identified a variant on chromosome 5 at 5q35 (rs60200309-A), close to the dedicator of cytokinesis 2 gene (DOCK2), which was associated with severe COVID-19 in patients less than 65 years of age. This risk allele was prevalent in East Asian individuals but rare in Europeans, highlighting the value of genome-wide association studies in non-European populations. RNA-sequencing analysis of 473 bulk peripheral blood samples identified decreased expression of DOCK2 associated with the risk allele in these younger patients. DOCK2 expression was suppressed in patients with severe cases of COVID-19. Single-cell RNA-sequencing analysis (n = 61 individuals) identified cell-type-specific downregulation of DOCK2 and a COVID-19-specific decreasing effect of the risk allele on DOCK2 expression in non-classical monocytes. Immunohistochemistry of lung specimens from patients with severe COVID-19 pneumonia showed suppressed DOCK2 expression. Moreover, inhibition of DOCK2 function with CPYPP increased the severity of pneumonia in a Syrian hamster model of SARS-CoV-2 infection, characterized by weight loss, lung oedema, enhanced viral loads, impaired macrophage recruitment and dysregulated type I interferon responses. We conclude that DOCK2 has an important role in the host immune response to SARS-CoV-2 infection and the development of severe COVID-19, and could be further explored as a potential biomarker and/or therapeutic target.

b. COVID-19 risk assessment at the Tokyo 2020 Olympic Games

Murakami M[18], Miura F[19], Kitajima M[20], Fujii K[21], Yasutaka T[22], Iwasaki Y[22], Ono K[22], Shimazu Y[23], Sorano S[24], Okuda T[25], Ozaki A[26], Katayama K, Nishikawa Y[27], Kobashi Y[28], Sawano T[29], Abe T[23], Saito MM[30], Tsubokura M[18], Naito W[22], Imoto S: [18]Fukushima Medical University, [19]Ehime University, [20]Hokkaido University, [21]Kao, [22]National Institute of Advanced Industrial Science and Technology (AIST), [23]Southern TOHOKU General Hospital, [24]Nagasaki University, [25]Keio University, [26]Jyoban Hospital of Tokiwa Foundation, [27]Kyoto University, [28]Seireikai Group Hirata Central Hospital, [29]Sendai Open Hospital, [30]University of Nagasaki

The 2020 Olympic/Paralympic Games have been postponed to 2021, due to the COVID-19 pandemic. We developed a model that integrated source–environment–receptor pathways to evaluate how preventive efforts can reduce the infection risk among spectators at the opening ceremony of Tokyo Olympic Games. We simulated viral loads of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emitted from infectors through talking/coughing/sneezing and modeled temporal environmental behaviors, including virus inactivation and transfer. We performed Monte Carlo simulations to estimate the expected number of newly infected individuals with and without preventive measures, yielding the crude probability of a spectator being an infector among the 60,000 people expected to attend the opening ceremony. Two indicators, i.e., the expected number of newly infected individuals and the newly infected individuals per infector entry, were proposed to demonstrate the extent of achievable infection risk reduction levels by implementing possible preventive measures. A no-prevention scenario produced 1.5–1.7 newly infected individuals per infector entry, whereas a combination of cooperative preventive measures by organizers and the spectators achieved a 99% risk reduction, corresponding to 0.009–0.012 newly infected individuals per infector entry. The expected number of newly infected individuals was calculated as 0.005 for the combination of cooperative preventive scenarios with the crude probability of a spectator being an infector of 1 × 10−5. Based on our estimates, a combination of cooperative preventions between organizers and spectators is required to prevent a viral spread at the Tokyo Olympic/Paralympic Games. Further, under the assumption that society accepts < 10 newly infected persons traced to events held during the entire Olympic/Paralympic Games, we propose a crude probability of infectors of < 5 × 10−5 as a benchmark for the suppression of the infection. This is the first study to develop a model that can assess the infection risk among spectators due to exposure pathways at a mass gathering event.

c. COVID-19 wastewater surveillance implemented in the Tokyo 2020 Olympic and Paralympic Village

Kitajima M[31], Murakami M[32], Iwamoto R[33], Katayama H[34], Imoto S: [31]Hokkaido University, [32]Center for Infectious Disease Education and Research, Osaka University, [33]Shionogi & Co. Ltd., [34]Graduate School of Engineering, The University of Tokyo

Wastewater-based epidemiology (WBE), which has attracted attention as a COVID-19 surveillance tool,1 was implemented in the Tokyo 2020 Olympic and Paralympic Village in order to better understand COVID-19 incidence in the village.2 Between July 14 and September 8, 2021, 690 wastewater samples—361 and 329 samples collected via passive and grab sam-

pling, respectively—were collected from manholes in the village. We collected wastewater samples, in addition to clinical data (i.e., confirmed positive cases), from seven distinct areas comprising the entire residential buildings. The wastewater samples were examined for the presence and concentration of SARS-CoV-2 RNA using a highly sensitive reverse transcription (RT)-qPCR-based detection method. We tested for SARS-CoV-2 RNA in wastewater and reported data daily to the Tokyo Organising Committee of the Olympic and Paralympic Games. The reported data were used as one of the indicators reflecting COVID-19 incidence to support judgement of the need for enhanced infection prevention measures.

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