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, 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, Nakagawa S, 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, Kawabata K, 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 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, Hyugaji T, Ono Y, Ito S, 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 Microflora

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. An enterococcal phage-derived enzyme suppresses graft-versus-host disease

Fujimoto K, Hayashi T[7], Yamamoto M, Sato N, Shimohigoshi M[7], Miyaoka D[7], Yokota C[7], Watanabe M[7], Hisaki Y[7], Kamei Y[7], Yokoyama Y[7], Yabuno T[7], Hirose A[7], Nakamae M[7], Nakamae H[7], Uematsu M, Sato S[7], Yamaguchi K, Furukawa Y, Akeda Y[8], Hino M[7], Imoto S, Uematsu S: [7]Osaka Metropolitan University, [8]National Institute of Infectious Diseases.

Changes in the gut microbiome have pivotal roles in the pathogenesis of acute graft-versus-host disease (aGVHD) after allogenic haematopoietic cell transplantation (allo-HCT). However, effective methods for safely resolving gut dysbiosis have not yet been established. An expansion of the pathogen Enterococcus faecalis in the intestine, associated with dysbiosis,

has been shown to be a risk factor for aGVHD. Here we analyse the intestinal microbiome of patients with allo-HCT, and find that E. faecalis escapes elimination and proliferates in the intestine by forming biofilms, rather than by acquiring drug-resistance genes. We isolated cytolysin-positive highly pathogenic E. faecalis from faecal samples and identified an anti-*E. faecalis* enzyme derived from *E. faecalis*-specific bacteriophages by analysing bacterial whole-genome sequencing data. The antibacterial enzyme had lytic activity against the biofilm of *E. faecalis* in vitro and in vivo. Furthermore, in aGVHD-induced gnotobiotic mice that were colonized with *E. faecalis* or with patient faecal samples characterized by the domination of *Enterococcus*, levels of intestinal cytolysin-positive *E. faecalis* were decreased and survival was signiffcantly increased in the group that was treated with the *E. faecalis*-specific enzyme, compared with controls. Thus, administration of a phage-derived antibacterial enzyme that is specific to biofilm-forming pathogenic *E. faecalis*—which is difficult to eliminate with existing antibiotics—might provide an approach to protect against aGVHD.

3. Health Medical Data Science

a. Intricate interactions between fine-scale genetic structure, lifestyle, and dietary habits in the Japanese population

Chen Y, Katayama K, Ishida S[9], Imoto S: [9]DeNA Life Science, Inc.

The fine-scale genetic structure within populations, focusing on demographic histories and migration patterns, has been explored previously. However, limited attention has been paid to understanding how genetic structure influences lifestyle and dietary habits within an epidemiological framework. This study explores the fine-scale genetic structure within a homogeneous Japanese population using advanced unsupervised learning techniques—Principal Component Analysis (PCA), Uniform Manifold Approximation and Projection (UMAP), and Density-Based Spatial Clustering of Applications with Noise (DBSCAN)—coupled with direct-to-consumer genetic testing data. We investigate the associated genetic factors and examine the relationship between the genetic structure and geographic ancestry. Additionally, using cross-sectional data and multinomial logistic regression, we further elucidate the nuanced impacts of lifestyle and dietary factors across genetic clusters, emphasizing the importance of integrating genetic data with epidemiological research. This study introduces a new framework for genetic epidemiology that considers both genetic and environmental influences.

b. Patch-level phenotype identification via weakly supervised neuron selection in sparse autoencoders for CLIP-derived pathology embeddings

Tamura K[10], Zhang Y-Z, Okubo Y, Imoto S: [10]Hiroshima University School of Medicine

Computer-aided analysis of whole slide images (WSIs) has advanced rapidly with the emergence of multi-modal pathology foundation models. In this study, we propose a weakly supervised neuron selection approach to extract disentangled representations from CLIPderived pathology foundation models, leveraging the interpretability of sparse autoencoders. Specifically, neurons are ordered and selected using whole-slide level labels within a multiple instance learning (MIL) framework. We investigate the impact of different pre-trained image embeddings derived from general and pathology images and demonstrate that a selected single neuron can effectively enable patch-level phenotype identification. Experiments on the Camelyon16 and PANDA datasets demonstrate both the effectiveness and explainability of the proposed method, as well as its generalization ability for tumor patch identification.

c. Diffusion model for imputing time-series gut microbiome profiles using phylogenetic information and metadata integration

Seki M, Zhang YZ, Imoto S.

The gut microbiota interacts closely with the host, playing crucial roles in maintaining health. Analysing time-series genomic data enables the investigation of dynamic microbiota changes. However, missing values create significant analytical challenges. We propose a microbiome imputation framework based on a conditional score-based diffusion model, tailored to microbiome data by incorporating phylogenetic convolutional layers. Our method effectively reduces mean absolute error across various missing data ratios for both 16S rRNA and whole-genome shotgun profiles. The imputed datasets enhance downstream predictive tasks, achieving area under the curve scores that exceed or are comparable with those of the existing methods. To further improve the performance, we embedded host metadata into the model using a tabular encoding approach, which yielded additional improvements particularly under higher missing ratios. Our findings underscore the potential of the diffusion model for processing time-series microbiome data with missing values.

4. COVID-19

a. Quantitative association of SARS-CoV-2 in wastewater and clinically confirmed cases in different areas of the Tokyo 2020 Olympic and Paralympic Village

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International mass gathering events, such as the Olympic and Paralympic Games, face the risk of cross-border transmission of infectious diseases. We previously reported that wastewater-based epidemiology (WBE), which has attracted attention as a COVID-19 surveillance tool, was implemented in the Tokyo 2020 Olympic and Paralympic Village to gain a comprehensive understanding of COVID-19 incidence in the village. In the present study, we explored the quantitative association of wastewater viral load and clinically confirmed cases in various areas of the village. From July 14 through September 8, 2021, 360 passive samples and 329 grab samples were collected from seven distinct areas within the village through manholes and examined for SARS-CoV-2 RNA by the Efficient and Practical virus Identification System with Enhanced Sensitivity (EPISENS) methods. The detection rates of SARS-CoV-2 RNA in passive and grab samples showed a significant association ($P < 0.001$, $\varphi = 0.32$, chi-square test), with passive sampling showing higher positive rate. Based on the Receiver Operating Characteristic (ROC) curve analysis on the wastewater viral load and clinically confirmed cases, the most sensitive cutoff point was judged to be the limit of quantification (LOQ) for the passive three-day samples. Under this optimal condition, the sensitivity and specificity were 0.78 and 0.40, respectively. The present study demonstrated the effectiveness of passive sampling for building-level wastewater surveillance based on the quantitative analysis of wastewater viral load and reported cases. Wastewater surveillance can be a powerful tool to monitor the incidence of infectious diseases among temporary residents, such as tourists and participants in international mass gathering events, provided that proper analytical methods and quantitative cutoff point are employed.

b. Comparison of COVID-19 testing strategies and costs for professional sports teams: A case study of J. League clubs

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Professional sports teams are entertainment groups that earn income through performances, and they recognize that efforts to prevent the within-team spread of infection that could lead to performance cancellation are important. Infectious disease control involves several costs, some of which are in a trade-off relationship. For example, frequent testing can reduce the spread of infection, but it also leads to increased costs. On the other hand, limiting the number of tests can reduce testing costs, but it increases the revenue loss from players becoming infected and the loss from canceling games. Therefore, a methodology that strikes a reasonable balance between the cost of control measures and the risk of infection is needed. The relationship between infection control measures and the number of infected individuals was investigated through simulations using the susceptible-exposed-infected-recovered (SEIR) model. Two types of testing scenarios as control measures were principally considered: rapid antigen testing or the slower PCR testing (regular-testing scenarios); and regular testing with more frequent, additional testing after the appearance of an infected individual (additional-testing scenarios). Testing fees, revenue loss due to player or staff inactivity as a result of infection, and expenses for postponement or cancelation of matches were considered as costs. Regular antigen testing was found to be more effective than PCR testing in reducing the number of infected individuals and associated costs. There are two main reasons why antigen testing was more efficient: It is less expensive than PCR testing; and the results are available sooner (immediately, versus at least a day of waiting time for the PCR results). This was shown to markedly reduce the number of infected individuals.

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