Individual Differences

Understanding the mechanisms of sex and individual differences and advancing prediction technology

Research and Development Objectives

Towards elucidating and predicting sex and individual differences and intrapersonal changes — A departure from the conventional practice of medical care based on patient averages

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The manifestations of various symptoms of our diseases and health conditions vary not only between the sexes and between individuals, but also even within the same person at different stages of life. Significant individual differences are also sometimes observed in the effects and side effects of medicines and other drugs. Following the experience of the new coronavirus infection (COVID-19), the public interest in sex and individual differences has urgently increased. However, current medical and health research is mainly based on population averages, and the medical care that many people receive is not always optimized for the individual. The first step approaching to the issues is to understand the mechanisms of gender and individual differences in specific symptoms, diseases, and health conditions at the molecular level. Based on this information, new treatment and prevention methods need to be developed that are optimized for the individual, such as precise stratification for specific diseases and the development of predictive models at the individual level.

In this research and development area, basic and clinical medical researchers, experimental biologists, epidemiologists, computer scientists and mathematicians, as well as measurement and information technology researchers, will work closely together, combining latest knowledge and technologies from different fields to integrate and analyze multi-level data at the molecular, cellular, tissue, organ, individual and population levels.

The project aims to elucidate the mechanisms by which individual and sex differences in health and disease, as well as changes within the same individual, are generated, and to develop optimal treatment and prevention technologies for individuals by constructing accurate stratification of pathological states and predictive models at the individual level.

AMED-CREST Started in 2024 — 1st period

Understanding the molecular basis governing individual differences of health-span and developing aging-prediction technology

ISHITANI Tohru
Professor, Research Institute for Microbial Diseases, The University of Osaka

There are individual and sex differences in lifespan and healthspan, making it difficult to measure the degree of aging or remaining lifespan based on age alone. In this study, we aim to understand the molecular mechanisms underlying individual and sex differences in lifespan and healthspan and to create aging prediction technology by conducting data-driven research that complements humans and ultra-rapid aging animals. In addition, by discovering quantitative aging markers and anti-aging molecules, we aim to create personalized medical technology seeds that can detect signs of aging in individual humans and extend healthspan.

Elucidation and control of the cellular microenvironment that produces sex and individual differences through deep learning

SHIMAMURA Teppei
Professor, Medical Research Laboratory, Institute of Integrated Research, Institute of Science Tokyo

This research develops an analytical platform using deep learning and next-generation small molecule inhibition technologies to analyze multi-scale, multi-modal data related to sex and individual differences. By elucidating differences in cellular states and microenvironments, their determinants, and possibilities for personalized therapies, we aim to accelerate disease research discovery and verification. We will validate the platform using osteoarthritis and intractable gastrointestinal cancers as targets, aiming to develop new treatments and prognosis prediction models that consider sex and individual differences, ultimately contributing to the realization of personalized medicine.

Multi-omics analysis for elucidating the difference between maternal and paternal genetic traits and its application to the prediction of obesity and diabetes

SUZUKI Yutaka
Professor, Graduate School of Frontier Sciences, The University of Tokyo

We aim to gain a deep understanding of the molecular mechanisms underlying sex differences, individual differences, and intra-individual changes, which will serve as the basis for future medical applications and prediction of unaffected diseases.
We will make full use of biological samples and genome data accumulated at BioBank Japan and Tohoku Medical Megabank Organization, the most representative biobanks in Japan.
We will conduct an intensive and precise multi-omics analysis of umbilical cord blood as an example of tissue in which newborns begin to express their own genes for the first time, we will attempt to elucidate the diversity of sex differences in genetic traits.

Development of predictive models and novel therapies based on sex and individual differences for cardiovascular disease

MIYAGAWA Shigeru
Professor, Graduate School of Medicine, The University of Osaka

Cardiovascular disease is one of the leading causes of death in Japan, with its progression being profoundly affected by sex and individual variability. Our objective is to develop predictive models for cardiovascular diseases, mainly heart failure and aortic aneurysm, through the integration of multi-omics analysis of tissue and blood samples, lifestyle data, clinical data, and the latest artificial intelligence technology, as well as a data distribution platform capable of distributed federated learning. We also aspire to develop novel therapeutic strategies by elucidating the underlying pathological mechanisms through comprehensive omics analysis.

Integrated understanding of sex-dependent biomodulation mechanisms associated with the interaction of circadian and seasonal rhythms and application to prediction technology

YASUO Shinobu
Professor, Faculty of Agriculture, Kyushu University

Mood and physical conditions in humans are regulated by interactions between circadian rhythms, seasonal rhythms, and menstrual rhythms in menstruating women. However, the interactions among multi-scale rhythms still need to be clarified. A series of our studies, a collaborative effort between experimental and mathematical researchers, aims to elucidate the interaction mechanisms underlying sex-dependent multi-scale rhythms and search for biomarkers to evaluate the interactions. Our goal is to develop a technology that can predict multi-scale-rhythm-associated symptoms such as winter depression and premenstrual syndrome.

AMED-CREST Started in 2025 — 2nd period

Linking Genomic and Individual Diversity through Tissue Architecture Across Individuals and Sexes

ISHIKAWA Shumpei
Professor, Graduate School of Medicine, The University of Tokyo

The architecture of biological tissues is governed by complex cellular interactions and further modulated by inter-individual genomic variation, leading to phenotypic diversity. In this study, we aim to elucidate inter-individual and sex-specific differences in tissue architecture and their genomic determinants, a domain that has been difficult to quantify and interpret. Leveraging proprietary deep learning methodologies and large-scale genomic pathology cohorts, we will systematically characterize these variations. Furthermore, we will interrogate the functional aspects of tissue architecture and identify conserved structural features that are preserved across species, thereby providing fundamental insights into the genomic regulation and evolutionary conservation of tissue organization.

Creating an Interpretable Genome Function Simulator

OKI Shinya
Professor, IRDA, Kumamoto University

Most disease-associated SNPs are located in noncoding regions, making it difficult to elucidate disease mechanisms. In this study, we will create an AI model that learns the relationship between genome sequences and public epigenomics data. We will also construct a simulator that predicts chromatin and gene expression changes caused by SNPs. Through verification experiments using MPRA, introducing mutations in mice, and analyzing human samples with SNPs, we aim to elucidate disease mechanisms based on individual differences in chromatin changes.

Multilayered analysis of lifestyle-related diseases based on macrophage continuum shaped by G×E interactions

SATOH Takashi
Professor, Graduate School of Medical and Dental Sciences, Institute of Science Tokyo

This study aims to elucidate the molecular mechanisms underlying sex- and individual-specific differences in obesity and type 2 diabetes from the perspective of the "macrophage continuum," in which macrophage functions undergo continuous changes driven by the interaction between genetic predisposition (SNPs) and environmental factors (such as lifestyle and life stage). Through integrated analyses of genomic and epidemiological cohorts, together with validation using human clinical samples and disease models, we seek to identify novel disease susceptibility molecules and develop innovative biomarkers and risk prediction models for lifestyle-related diseases.

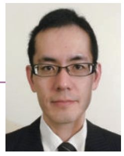
Analysis of the influence of "individual variations" in the local microbiome of the gut on the acquired colorectal cancer predisposition and the development of strategies for its suppression

YACHIDA Shinichi
Professor, Graduate School of Medicine, The University of Osaka

Histologically unremarkable colorectal mucosa in cancer patients often exhibits an acquired predisposition to colorectal cancer, having previously accumulated epigenetic and genomic alterations prior to tumor onset. The purpose of this study is to precisely identify the bacterial communities within the local mucosal environment that promote tumor development. We aim to establish a robust framework by integrating advanced bioinformatics and AI to precisely diagnose the differences in predisposition to acquired colorectal cancer between individuals and sexes, based on microbial profiles, which will inform the core concepts of precision preemptive medicine and facilitate the development of new cancer prevention strategies.

PRIME Started in 2024 ······ 1st period

The realization of preemptive medicine through the elucidation of cardiovascular complex disease systems driven by the integration of static and dynamic omics



ITO Kaoru
Professor,
Graduate School of Medicine, Chiba University

Cardiovascular complex diseases are complicated conditions that arise from intricate interactions between genetic and environmental factors, with significant influences from individual and sex differences. In this research project, we will integrate dynamic omics data with pioneering artificial intelligence, alongside genomic and clinical information, to achieve a comprehensive understanding of these individual and sex differences in disease. Simultaneously, we will establish and validate methods for stratifying disease risk in individuals who have not yet developed the disease. Ultimately, our goal is to build and implement a precision medicine system that proposes preventive measures tailored to various stages, from health to pre-disease and disease onset.

Single nucleotide resolution analysis and prediction of gene regulatory elements by saturation mutagenesis MPRA

INOUE Fumitaka
Associate Professor,
WPI-ASHBi, Kyoto University

Genetic factors responsible for diseases, individual differences, and evolution are more likely to be found in gene regulatory elements in the non-coding genome, rather than in coding regions. In this project, we utilize the Massively Parallel Reporter Assay (MPRA), which enables us to characterize enhancer functions in a high-throughput manner and at single-nucleotide resolution, to predict the effects of single nucleotide variants on gene regulation. Through this approach, we aim to understand the molecular mechanisms underlying diseases and individual differences.

Space-time proteomics with single-cell resolution enabled by next-generation proteome sequencer

KANAO Eisuke
Assistant Professor, Graduate School of Pharmaceutical Sciences, Kyoto University

This research aims to completely renovate bottom-up proteomics technologies from the perspective of separation science and materials chemistry, developing a "next-generation" proteome sequencer. Furthermore, this technology will be applied for time-lapse analysis of single cells and spatial proteomics. Based on these technologies, we will capture the proteome changes during early development with unprecedented resolution as the first step toward understanding the mechanisms of sex and individual differences.

Investigating individual differences by human population-scale cell culture and time-series multi-omics

KOJIMA Shohei
Project Associate Professor, Human Biology-Microbiome-Quantum Research Center, Keio University

I will employ a miniaturized human population cell culture system to conduct time-series multi-omics analyses and statistical genetics. This approach aims to unravel the complex human genetics and biology underlying the emergence of human phenotypic differences that cannot be understood by snapshot research. This work will bridge the gap between real-world studies in biobanks and laboratory-based mechanistic research, and generate basic research data that forms the foundation for improved disease prediction and precision medicine.

Study for individual differences of A-to-I RNA editing

SAKURAI Masayuki
Associate Professor, Research Institute for Biomedical Sciences, Tokyo University of Science

A-to-I RNA editing has the same effect as base substitution or mutation from A to G, but is a change in genetic information that is not described in the genomic information. It is highly possible that unexplained individual and sex differences may result from differences in editing, which in turn may include differences that affect cancer incidence, disease incidence, life span, and health. This project aims to clarify this, to accumulate information on A-to-I RNA editing sites, and to construct an editome database.

Study of development of prediction platforms for progression of lung cancers based on differential omics backgrounds among sex and individual differences

SUZUKI Ayako
Associate Professor, Graduate School of Frontier Sciences, The University of Tokyo

This study aims to develop a predictive platform of lung cancer progression by integrating spatial omics techniques, human lung organoids and gene expression network analytical methods. We will measure the omics background of cells that reflect individual differences, as well as their responses to endogenous and exogenous stress stimuli. We will analyze detailed information of aberrant differentiation statuses of lung cancer cells at omics levels and utilize it for prediction of lung cancer progression.

Development of functional connectivity analysis method using deep learning and estimation of individual traits and neuropsychiatric disorders

CHIKAZOE Junichi
Professor, Center for Brain, Mind and Kansei Sciences Research, Hiroshima University

This research aims to establish new analytical methods for resting-state fMRI data to develop objective indicators for diagnosing mental disorders. We will use multilayer perceptrons and Transformer models to examine functional connections between brain regions and construct individual characteristic estimation models. Additionally, we will create diagnostic algorithms for neuropsychiatric disorders using data from the AMED Brain/MINDS Beyond project. We particularly focus on methods for utilizing deep learning in biological data with limited sample sizes.

Mechanisms underlying heart failure pathogenesis through the lens of inter-individual variability of hematopoietic clonal divergence

NAKAYAMA Yukiteru
Project Leader, Department of Clinical Medical Science, Tokyo Metropolitan Institute of Medical Science

Persistent inflammation following the immune response against external cardiac stress underlies incident heart failure. We have recently reported that heart failure induces the phenotypic modulation of hematopoietic stem cells, immmature cells that all types of blood cells originate from. We hypothesize that individual differences of immune response at the level of hemaotopoietic stem cells would determine inter-individual variability in risks of incident heart failure. We will analyze the differences in bone marrow niches as well.

Understanding the impact of differential sex chromosome states on cellular phenotypes

YOKOBAYASHI Shihori
RIKEN ECL Team Leader, RIKEN Center for Integrative Medical Sciences

The sex chromosome composition in the human genome is typically the XX type in females and the XY type in males, and one X chromosome in females is epigenetically silenced to compensate for the differences in gene dosage. In this study, I aim to understand sex differences at a cellular level by elucidating the impact of sex chromosome composition or conversion/instability in the X-chromosome epigenome status on cellular phenotypes and functions.

Precision stratified treatment based on individual differences due to retrotransposon-based insertion polymorphisms

YOSHIMI Akihide
Chief, Division of Cancer RNA Research, National Cancer Center Research Institute

Transposable elements (TEs), also known as jumping genes, are known to make up about 46% of the human genome. In this project, we aim to investigate the impact of individual differences due to TE insertion polymorphisms on treatment outcomes and prognosis of cancer patients, and to refine prognosis and treatment response prediction systems by identifying new biomarkers. Additionally, by elucidating the mechanisms of expression, we aim to develop treatment methods and propose stratified treatments based on individual differences in TE insertion polymorphisms.

PRIME Started in 2025 — 2nd period

Decoding the Essence of Sexual Dimorphism in Adipose Tissue through Cellular Lineage and Temporal Dynamics

IKUSHIMA Yoshiko M
Lecturer, SiRIUS Institute of Medical Research, Tohoku University

White adipose tissue exhibits marked sex differences; for instance, men tend to accumulate more visceral fat, a key risk factor for metabolic syndrome. However, the mechanisms underlying these differences remain unclear. Our research explores sex differences in the origin, composition, and characteristics of white adipocytes at the single-cell level. We aim to uncover how cellular-level sex differences in adipocytes contribute to the sexual dimorphism observed in white adipose tissue biology and systemic metabolism. Building on these insights, we seek to propose sex- and age-specific preventive or therapeutic strategies for metabolic disorders.

Stratification of genetic risks of immune-mediated diseases and development of pathway-specific genetic risk score

OTA Mineto
Lecturer, The University of Tokyo Hospital

Immune-mediated diseases exhibit a rich diversity in their pathophysiology, even within the same condition, and the treatment responses vary among patients. However, it is still unclear which molecular biological pathways contribute to this diversity. In this study, we aim to elucidate the molecular pathologies that lead to this diversity by combining genome-wide association study data with experimental functional genetics data. Furthermore, we aim to develop a method to quantify immunological individual differences for each patient based on this information.

Regulation of Urothelial Carcinoma Invasion Based on Sex-Dependent Inflammatory Control and Tissue Remodeling Mechanisms: Toward Clinical Applications

KAWASHIMA Atsunari
Associate Professor, Graduate School of Medicine, The University of Osaka

Urothelial carcinoma occurs more frequently in men, while women are more often affected by advanced disease with poor prognosis; however, the reasons for this remain unclear. We utilize our uniquely established model in which upper urinary tract cancer spontaneously develops specifically in BALB/c female mice to elucidate the underlying causes. By applying these findings to humans, we aim to realize cancer care tailored to sex differences, enabling more accurate diagnosis and effective treatment.

Disease Forecasting and Optimal Intervention Exploration Using a Spatiotemporal Omics Simulator for Tumor Tissue

KOJIMA Yasuhiro
Laboratory Head, National Cancer Center

With innovations in single-cell and spatial omics, we are increasingly able to capture the state of tumor tissues at the time of observation in great detail. However, our understanding of how inter-individual differences at the tissue level arise remains fragmented. In this study, we aim to reconstruct three-dimensional transcriptomes from pathology images and develop a spatiotemporal omics simulator that incorporates cell–cell interactions and gene regulatory networks. This will enable spatiotemporal prediction of future pathological states in individual patients and the proposal of optimal interventions.

Study of differences of genetic causals of motor neuron defects among individual sporadic ALS by using cost-effective single-cell functional genomics and disease-specific iPS cell bank

SHICHINO Shigeyuki

Lecturer, Research Institution of Biomedical Sciences, Tokyo University of Science

Amyotrophic lateral sclerosis (ALS), a disease characterized by motor neuron dysfunction and eventual total paralysis, is known to arise from diverse genetic backgrounds. However, the relationship between an individual's genetic background and the mechanisms leading to motor neuron dysfunction remains unclear. This study aims to elucidate the causal relationship between genetic background variability and motor neuron dysfunction induction. This will be achieved through comprehensive intervention targeting thousands of genes using scRNA-seq/SNP data from dozens of unique ALS-derived iPS cells and a newly developed low-cost single-cell Perturb-seq method.

Investigation of inter-individual differences in brain development and diseases that are driven by sequence polymorphisms in dark matter genomic regions

SUZUKI Ikuo

Associate Professor, Graduate School of Science, The University of Tokyo

The human genome has been fully sequenced, yet the so-called “dark matter regions,” which include duplicated sequences, remain insufficiently understood. These regions are expected to contain human-specific genes as well as polymorphisms associated with individual differences in the brain and susceptibility to disease. With advances in omics technologies such as long-read sequencing, their analysis has become feasible. In this study, we aim to comprehensively identify polymorphisms in duplicated genes and other elements within dark matter regions, and to clarify their relationships with brain development, cognitive functions, neurodevelopmental disorders, and tumor progression.

Inferring neural activity-responsive dynamics from snapshot single-cell data: applications to studies of psychiatric disorders and genetic basis of interindividual differences

TAKATA Atsushi

Team Director, RIKEN Center for Brain Science

It is well established that genetic factors contribute to the risk of psychiatric disorders; however, these conditions cannot be fully explained by DNA sequences, which are essentially invariant throughout life, and their clinical courses are highly fluctuating. In this study, we will develop a method to extract the "dynamic" components of neural activity responses from single-cell expression data, which otherwise provide only a "static" snapshot of the transcriptome. By applying this approach, we aim to elucidate the pathophysiology of psychiatric disorders, identify novel therapeutic targets, and advance our understanding of the molecular basis underlying individual differences.

Strain-resolved gut microbiome analysis for human disease associations

NISHIJIMA Suguru

Project Associate Professor, Graduate School of Frontier Sciences, The University of Tokyo

In this study, I will develop a novel computational pipeline capable of accurately estimating gene content at the strain level for gut bacteria. By applying this method to large-scale metagenomic datasets, I aim to comprehensively reveal the occurrence patterns of strain-specific genes associated with various diseases. This will contribute to the identification of new biomarkers and therapeutic targets for personalized medicine based on individual differences in gut bacterial strains.

Study of Brain AMPA Receptor Dynamics and Diagnostic Support Technology Based on Individual Differences during Menopause

HATANO Mai

Assistant professor, Yokohama City University Graduate School of Medicine

This study aims to elucidate, at the molecular level, how the rapid hormonal changes that occur during menopause affect AMPA receptors in the human brain, using the AMPA receptor–specific PET ligand [^{11}C]K-2. By integrating serum hormone concentrations and validated menopause symptom scales, we will advance the understanding of the heterogeneous pathophysiology of menopausal disorders. Furthermore, we will develop machine learning–based diagnostic support models to contribute to improved understanding of menopause and the advancement of personalized medicine.

Innovative Therapeutic Strategies for Autoimmune Diseases:Unveiling the Impact of Diversity on T cell Responses to Neoself

MORI Shunsuke

Assistant Professor, Research Institute for Microbial Diseases, The University of Osaka

Dysfunction of MHC class II molecule leads to the presentation of "neoself," an autoantigen with abnormal antigenicity. Neoself is recognized by T cells as non-self, thereby inducing autoimmunity. It has become clear that the induction of neoself is influenced by sex and individual differences. In this study, we aim to elucidate the expression mechanism of neoself involving sex and individual differences, and thereby establish novel therapeutic strategies for autoimmune diseases, including radical treatments that target the root cause of the disease.