NTU College of Public Health
30th Anniversary and
International Symposium

2023 KP Chen Memorial Lecture

— Triangulation of Evidence —

Professor
George Davey Smith

2023 KP Chen Memorial Lecture

Time | 2023.10.20 10:00-12:00 (Friday)
Venue | Room 101, College of Public Health, National Taiwan University

International symposium on analytics and applications of multiomics data in public health

Time | 2023.10.20 13:30-17:00 (Friday)
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10:00-10:15	Award Ceremony
10:15-11:15	Keynote speech: Triangulation of Evidence Prof. George Davey Smith
11:15-11:55	Panel Discussion Prof. George Davey Smith (University of Bristol) Prof. Fumihiko Matsuda (Kyoto University) Prof. Pak Chung Sham (The University of Hong Kong) Prof. Wei J. Chen (National Taiwan University)
11:55-12:00	Group Photo

International symposium on analytics and applications of multiomics data in public health

Time | 2023.10.20 13:30-17:00 (Friday)
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13:30-14:10	Steven E. Hyman (Harvard Department of Stem Cell and Regenerative Biology)
14:10-14:50	Pak Chung Sham (Department of Psychiatry, The University of Hong Kong)
14:50-15:10	Tea Break
15:10-16:00	Fumihiko Matsuda (Center for Genomic Medicine, Kyoto University)
16:00-16:40	Fann, Cathy S.-J. (Institute of Biomedical Sciences, Academia Sinica)
16:40-16:50	Closing Remark

- **Professor of Clinical Epidemiology**
- **Director, MRC Integrative Epidemiology Unit, Bristol Medical School, University of Bristol, Bristol, UK**

Prof. GEORGE DAVEY SMITH

FRS, MD, DSc, MSc, FMedSci, FRCP, FFPH

1981: BA, Queen's College, Oxford

1984: MB BChir, from Jesus College, Cambridge

1988: MSc, ondon School of Hygiene and Tropical Medicine

1991: MD, Jesus College, Cambridge

2000: DSc, Queen's College, Oxford

Professor George Davey Smith is a clinical epidemiologist who has focused on methods for improving causal inference in studies of disease aetiology and disease prevention. His work has involved early implementation of ‘negative controls’ in epidemiological studies, the use of cross-context comparisons, sensitivity analyses, unobtrusive data collection methods and randomized trials in thought-to-be difficult situations. He pioneered the use of germline genetic variants for investigating modifiable causes of disease (‘Mendelian randomization’), developed several extensions of the basic method, and contributed to its application in many settings. He is an advocate of the pre-specified application of a range of methods, with different structures of potential biases, to the same question (‘triangulation’), as the key approach to strengthening causal inference. Throughout his career he has promoted increasing the accessibility of data, and implemented this in studies he has led, including the Avon Longitudinal Study of Parents and their Children (ALSPAC).

CV

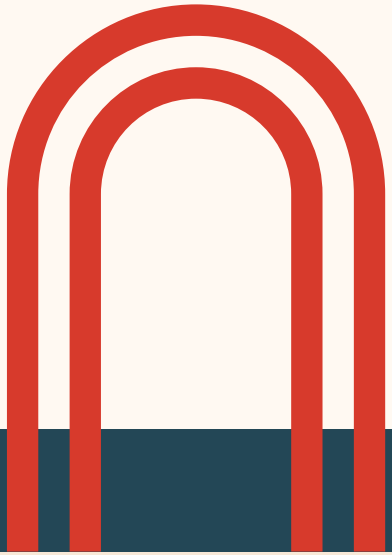
Professor George Davey Smith

SPEECH TOPIC

TRIANGULATION OF EVIDENCE

ABSTRACT

Aetiological epidemiology is concerned with the identification of causal influences on disease risk. Randomized controlled trials are, when possible, the cornerstone of knowledge as to whether interventions based on aetiological studies are merited. It is not feasible to subject all of the many candidate causes to large-scale RCTs, however, even in situations where they are in principle possible. Triangulation of evidence is an approach that attempts to formally combine findings from different domains to strengthen causal inference. Triangulation embraces the variety of evidence thesis, that inferential strength depends not only on the quantity of available evidence, but also on its variety: the greater the variety, the stronger the resulting support. An essential condition is that the systematic errors and biases are unrelated across different study types. For example, the effect of raising circulating HDL cholesterol on the risk of coronary heart disease can be estimated from RCTs or through Mendelian randomization using genetic variants related to HDL level. Both the results of RCTs and Mendelian randomization studies could be biased. However, the potential biases in one study design would not influence estimates from the other approach: the biases are unrelated to each other. In observational epidemiology approaches that can be applied include the use of negative control exposures or outcomes; the deliberate use of data from contexts in which confounding structures differ; the use of instrumental variables and related approaches, such as regression discontinuity; quasi-experimental studies; the estimation of the expected magnitude of associations generated by confounding and the incorporation of mechanistic data, amongst others. Pre-registration of protocols for the triangulation of evidence increases confidence in the findings produced.



- **Professor, Kyoto University Graduate School of Medicine**
- **Principal Investigator of the Nationwide Rare Disease Platform program, AMED**
- **Knight of the National Order of Merit**

Prof. FUMIHIKO MATSUDA

1990: PhD, Kyoto University Graduate School of Medicine
1998: Head of gene identification, Centre National de Genotypage in Evry, France
2003: Professor, Kyoto University Graduate School of Medicine
2007: Directeur de Recherche, Institut national de la santé et de la recherche médicale
2017: Pincipal Ivestigator, Nationwide Rare Disease Platform program financed by the Japan Agency of Medical Research and Development
2021: Knight of the National Order of Merit (Chevalier de L'Ordre National de Mérite)

Professor Fumihiko Matsuda obtained his Ph.D. from Kyoto University Graduate School of Medicine in 1990 under Professor Tasuku Honjo and continued his research with him until 1998. Throughout this period, his work is the organization of the human immunoglobulin heavy-chain variable-region (VH) gene locus. In 1998, he joined the Centre National de Genotypage (CNG) in Evry, France, as the head of gene identification. During his ten-year stay at CNG, he played a significant role in numerous comprehensive genetic analyses of multigenetic disorders. Since holding a joint appointment as a Professor of the Center for Genomic Medicine at Kyoto University in 2003, he has focused on the trans-ethnic genetic studies of human diseases. Since 2012, he has led an international collaboration with McGill University in genomics and contributed to establishing an International Joint Degree Program in Genomic Medicine between Kyoto and McGill. The program was initiated in April 2018. He is currently the Dean of the Kyoto-McGill International Collaborative School of Genomic Medicine. Since 2017, he has served as the research director of RADDAR-J, a nationwide rare disease platform program in Japan supported by AMED.

Professor Matsuda has consistently devoted himself to researching human genetics and genomics by integrated omics analysis of human disorders through various positions he has engaged. He has experience working in France for ten years with international collaborators. He is also promoting international collaborations with Asian countries, including China, Korea, and Thailand, as well as with France, Canada, and the U.K.

Professor Matsuda is "Chevalier de l'Ordre National du Mérite".

Professor Fumihiko Matsuda

SPEECH TOPIC

THE ROLE OF THE INTEGRATIVE RARE DISEASE ANALYSIS PLATFORM OF JAPAN "RADDAR-J" TO ELUCIDATE THE PATHOLOGY OF RARE DISORDERS

ABSTRACT

There are more than 10,000 rare diseases globally. The total number of patients with rare disorders is 6-8% of the population, although the number of patients with each disorder is small. In Japan, approximately 300 research groups are responsible for epidemiological studies, establishing diagnostic criteria and guidelines, researching pathogenesis, and clinical trials of rare diseases. For cross-sectional research on rare diseases aiming to develop new treatments and new drugs, it is essential to consolidate and analyze a variety of high-quality information in an integrated manner.

To address this critical issue, we set out to establish an integrative rare disease analysis platform, "RADDAR-J", in FY2016. Through collaboration with 63 rare disease research groups, we have designed and constructed registries of 145 diseases and collected detailed clinical information on 25,184 cases by the rare disease research groups (as of September 2023). In addition, whole genome sequencing information on 4,449 cases and 7,674 controls, and comprehensive information on blood proteins (proteome) of 600 patients and 2,000 controls measured by Somascan were accumulated.

In this presentation, I will outline the overall picture of RADDAR-J and discuss the risk prediction of HTLV-1-related myelopathy (HAM/TSP) using the accumulated genomic and clinical information.

- **Chair Professor of Psychiatric Genomics, Li Ka Shing Faculty of Medicine, University of Hong Kong**

Prof. PAK CHUNG SHAM

BA, BM BCh, MRCPsych, MSc, PhD

Suen Chi-Sun Professor in Clinical Science

Director of Academic Developments, Psychiatry,

2006: Chair Professor of Psychiatric Genomics

2012: Director, Centre for Genomic Sciences

2014: Director, State Key Laboratory of Brain and Cognitive Sciences

LKS Faculty of Medicine, The University of Hong Kong

Professor Pak Sham is a world renowned expert in genetics and epidemiology of psychiatric disorders, statistical methodology for genetic and epidemiological studies. He is currently Chair Professor of Psychiatric Genomics, Director of Centre for Genomic Sciences and holds a named professorship as Suen Chi-Sun Professor of Clinical Science. In his early career, he was dually trained as specialist in psychiatry with The Royal College of Psychiatrists and PhD in Genetics at University of Cambridge. Being one of the most frequently cited scholar in psychiatric genetics, he authored more than 400 peer-reviewed articles and the internationally acclaimed book entitled “Statistics in Human Genetics” (Edward Arnold, London 1998).

CV

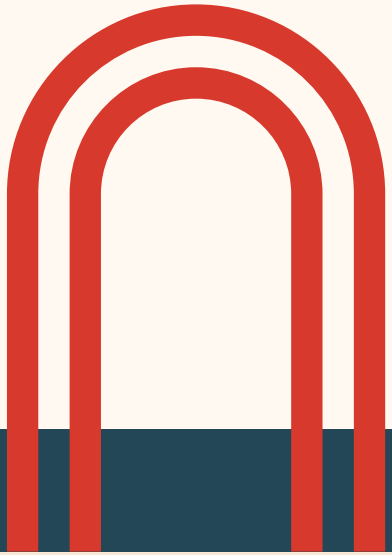
Professor Pak Chung Sham

SPEECH TOPIC

CAUSAL MODELLING IN PSYCHIATRIC PHENOTYPES

ABSTRACT

Psychiatric disorders are multifactorial phenotypes that result from the accumulation of genetic and environmental risk factors and their adverse impact on neural and psychological functioning. The identification of causal risk factors and intermediate phenotypes is needed for formulating effective prevention and intervention strategies for psychiatric disorders. I will review approaches for modelling causal factors, including structural equation modelling of twin data and Mendelian randomization, and their application to psychiatric disorders.



- **Vice President, Distinguished Investigator & Director, Center for Neuropsychiatric Research, National Health Research Institutes**
- **Distinguished Professor, Institute of Epidemiology and Preventive Medicine, College of Public Health, NTU**

Prof. WEI J. CHEN

ScD, MS, MD

1984: MD, Medicine, College of Medicine, National Taiwan University

1987: MS, Behavioral Sciences and Epidemiology, Harvard University

1992: ScD, Epidemiology, School of Public Health, Harvard University

Professor Wei J. Chen has served as Distinguished Researcher and Director of the Neurological and Psychiatric Research Center since January 2020. Professor Wei J. Chen graduated from the Department of Medicine, National Taiwan University School of Medicine in 1984, and received his PhD from the Institute of Epidemiology, Harvard School of Public Health in the United States in 1992. From 1993 to 1997, he served as an associate professor at the Institute of Epidemiology, School of Public Health, National Taiwan University (hereinafter referred to as the School of Public Health). From 1998 to 2004, he was appointed as the director of the Institute of Epidemiology. From 2005 to 2011, he was promoted to the deputy dean of the School of Public Health, and then served as the dean of the School of Public Health (2011-2017). In the last month of the dean's term (July 2017), the School of Public Health finally received accreditation from the Council on Education for Public Health (CEPH) after ten years of hard work, becoming the first accredited public school in Asia. Faculty of Health.

CV

- **Distinguished Service Professor of Stem Cell and Regenerative Biology, Harvard University**
- **Director of Stanley Center for Psychiatric Research at the Broad Institute**

Prof. STEVEN E. HYMAN

MD, MA, BA

1974: BA, Yale College, Yale University

1976: MA, University of Cambridge

1980: MD, Harvard Medical School, Harvard Medical School

Steven E. Hyman, M.D., is a Harvard University Distinguished Service Professor of Stem Cell and Regenerative Biology and a Core Institute Member of the Broad Institute of Harvard and MIT, where he directs the Stanley Center for Psychiatric Research. The Stanley Center engages in large-scale, globally conducted studies of neuropsychiatric genetics, stem cell biology, neurobiology, and technology development in support of translational efforts focused on reducing the global burden of psychiatric disorders.

Hyman has served as President of the Society for Neuroscience (2015), President of the American College of Neuropsychopharmacology (2018), founding President of the International Neuroethics Society (2008-2013), and Editor of the Annual Review of Neuroscience (2002-2016). He is a fellow of the American Academy of Arts and Sciences, a fellow of the American Association for the Advancement of Science, and a member of the National Academy of Medicine, where he served on the governing Council (2012-2018) and which he represented on the Governing Board of the National Research Council, the operating arm of the US National Academies of Sciences, Engineering, and Medicine (2016-2019). From 2012-2018 Hyman chaired the Forum on Neuroscience and Nervous System Disorders of the US National Academies, which brings together industry, government, foundations, patient groups, and academia. In 2016, he was awarded the Rhoda and Bernard Sarnat International Prize in Mental Health by the National Academy of Medicine.

CV

Professor Steven E. Hyman

SPEECH TOPIC

FROM GENETICS TO BIOLOGICAL INSIGHT IN SCHIZOPHRENIA, A PARADIGMATIC PSYCHIATRIC DISORDER

ABSTRACT

The biological mechanisms underlying psychiatric disorders long resisted elucidation, forcing reliance for treatment on a small number of serendipitously discovered drug classes. The revolution in genomic technology in the first years of the 21st century, however, made possible the successful identification of many common and rare DNA variants associated with these highly heritable conditions. The result has been progress toward mechanistic insight and the first steps toward biomarker discovery and new therapeutics. Illustrated by progress in schizophrenia, a paradigmatic and previously mysterious psychiatric disorder, I will discuss both progress and the many challenges that remain based on the complexity, heterogeneity, and inviolability of human brains and on the difficulty of developing disease models. Despite these challenges, a general approach, grounded in genetics and neurobiology, gives reason for optimism for better diagnosis and treatment of these highly distressing and disabling disorders.

- **Research Fellow / Professor, Institute of Biomedical Sciences, Academia Sinica. Taiwan**

Prof. CATHY SJ FANN

1988: MS Statistics. University of Iowa, USA

1993: PhD Biostatistics. University of Iowa, USA

1993: Research Associate. Columbia University, USA

1996: Assistant Professor, Albert Einstein College of Medicine, USA

2003: Associate Research Fellow, IBMS, Academia Sinica, Taiwan

2007: Research Fellow, IBMS, Academia Sinica, Taiwan

Professor Cathy SJ Fann is a genetic statistician, she is one of the pioneers in the field of statistical genetics in Taiwan. Her expertise is in the integration of advanced biostatistical and bioinformatics approaches. Her research covers a vast array of subjects in medical genetics, including disease gene identification, comparative genomics, population genetics, and phylogenetic evaluations. She addresses a multitude of health-related areas, from oncology and cardiology to neurology and metabolic disorders. While some of her scholarly articles introduce innovative methods for early disease detection, others investigate deep into the genetic basis of complex medical conditions. Utilizing a diverse set of statistical and genetic methods.

CV

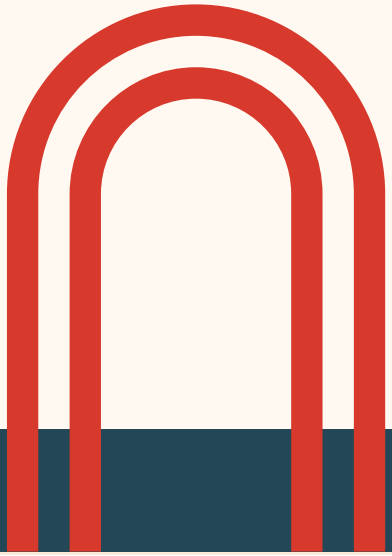
Professor Cathy SJ Fann

SPEECH TOPIC

BIG DATA APPLICATIONS IN GENETIC RESEARCH: USING TAIWAN AND UK BIOBANK

ABSTRACT

By analyzing from the Taiwan Biobank data, we identified 995 genetic regions associated with common diseases and traits. This included 135 regions that are unique to Taiwanese. We discovered shared genetic factors that play a role in these conditions. Within traits related to glycemic traits, we pinpointed 115 significant genetic regions, which included four new variations. To predict the risk of type 2 diabetes in Taiwanese individuals, we developed and validated genetic risk scores amplifying gene discovery and disease risk prediction for non-European populations. Furthermore, we delved into sub-types of Metabolic Syndrome (MetS) using data from the UK Biobank. Through unsupervised clustering, we unveiled distinct MetS endophenotypes and their connections to clinical outcomes. Genome-wide association studies (GWAS) highlighted relevant genetic traits. We established and validated endophenotype-specific polygenic risk score (PRS) models and identified potential drug targets, all of which were confirmed using data from the Taiwan Biobank



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