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Genomewide Association Studies in Pharmacogenomics: Meeting Report of the NIH Pharmacogenomics Research Network-RIKEN (PGRN-RIKEN) Collaboration

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Abstract

Genomewide association studies (GWAS) have resulted in the identification of many heritable genetic factors that underlie risk for human disease or variation in physiologic traits. In contrast, there are fewer GWAS of drug response phenotypes, despite extensive unexplained interindividual variability. To address this urgent need, the NIH Pharmacogenomics Research Network (PGRN) and the Center for Integrative Medical Sciences (IMS) at RIKEN support a collaboration, PGRN-RIKEN, with the goal of accelerating GWAS of drug response phenotypes.

Of the 2431 GWAS listed in the GWAS Catalog of NHGRI-EBI[1], only 182 (7.5%) are annotated as “pharmacogenomics/drug response,” and of these, the PGRN-RIKEN collaboration has supported 15 studies, representing 8% of the cataloged GWAS. Currently, the PGRN-RIKEN collaboration supports 41 projects and over 55,000 samples have been genotyped or sequenced. Each year, two meetings are held: one in Japan and one in the United States. In 2016, the U.S. meeting was held on April 20 and 21 in San Francisco. Below we provide a brief history of the PGRN-RIKEN collaboration and highlights of this years meeting.

The PGRN-RIKEN collaborative project was established in 2008, under the co-leadership of Yusuke Nakamura, Kathleen Giacomini, and Mark Ratain, and was funded partly by the National Institutes of Health (NIH) from 2010 to 2015 to support scientific meetings and to provide some support for genomewide genotyping. RIKEN IMS provided considerable

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resources and support in terms of genotyping core services and data analysis expertise. Since 2008, scientists from the PGRN (http://www.pgrn.org/pgrn-riken.html) proposed genomewide studies for pharmacogenomics research, which was based on collected DNA samples with associated drug response data (Figure 1). Scientists from both the PGRN and the IMS in Japan evaluated the proposals through peer-review with an opportunity for oral presentation at a bi-annual meeting alternating between the US and Japan. Top scored projects were selected for genomewide genotyping and associated data analyses. In the beginning of July 2015, the collaborative and funding models were modified. In particular, the collaboration has been expanded to allow any member of the PGRN (pgrn.org), to apply for a PGRN-RIKEN collaborative project. Funding from NIGMS supports a portion of the meetings in the US. The IMS continues to provide support for genotyping with rigorous criteria for selection of new projects. In the first round of proposals, four potential new projects for genomewide genotyping of large clinical pharmacogenomics samples were selected for presentation at the 2016 spring meeting in San Francisco; these projects are currently under review. Below we describe this fruitful collaboration and the additional scientific presentations in three major research areas of pharmacogenomics that were given at the PGRN-RIKEN meeting in San Francisco.

New Discoveries in Cancer Pharmacogenomics (Liu, Kroetz, Innocenti, Wang, Low)

Nineteen of the 41 projects supported through the PGRN-RIKEN collaboration are centered on identifying genetic risk factors for anti-cancer drug response and toxicity (see http://www.pgrn.org/riken-projects.html, Figure 2). Many of the supported studies involve samples obtained from National Cancer Institute's National Clinical Trials Network (NCTN) (http://www.cancer.gov/research/areas/clinical-trials/nctn). At the meeting, two of the presentations were related to discovering genetic factors that associate with efficacy to anti-cancer drugs and were focused on overall survival in ovarian cancer and colorectal cancer. Two additional presentations described genetic factors that predispose patients to risk for toxicities associated with anti-cancer drugs. Pathway analyses (e.g. KEGG, Reactome, Biocarta and Pathway Commons) from candidate pathways were used to test associations between particular pathways and drug toxicity. For example, in one presentation the association of rare variants in genes involved in the VEGF pathway with bevacizumab-induced hypertension was described. In addition to pathway analysis, presenters also described candidate gene analysis. For example, one investigator described a candidate gene study to test the hypothesis that sunitinib-induced thrombocytopenia is associated with a common reduced function variant (Q141K) in the transporter, ABCG2 (BCRP)[2]. Notably, the incidence of sunitinib-induced thrombocytopenia is higher in Asian populations, potentially due to a higher allele frequency of Q141K in Asians.

Functional Studies in Pharmacogenomics (Wang, Ahituv)

Identifying replication cohorts to validate findings from the discovery cohort remains a huge challenge in many pharmacogenomics GWAS. However, because the targets and pathways of many drugs are known, mechanistic studies are more tractable in pharmacogenomics

research. Investigators at this meeting presented novel methods and functional analyses to demonstrate the relevance of GWAS findings to associated pharmacological traits. Using cell line models, investigators at the Mayo Clinic described extensive and elegant functional studies to understand the role of the genes in the top loci identified in GWAS. New pharmacologic mechanisms, beyond inhibition of CYP19A1, for aromatase inhibitors were described. Methods described included use of siRNA to knockdown genes identified in GWAS to modulate expression levels of pharmacological targets[3, 4]. Furthermore, investigators in Mayo Clinic described the use of endophenotypes, such as estrogen and drug levels, to explain pharmacogenomic associations between key genes and response to aromatase inhibitors. Finally, Nadav Ahituv from UCSF, a keynote speaker at the meeting, described the use of RNA-Seq and ChIP-Seq to identify regulatory elements and genes, which are differentially expressed after drug exposures in cell lines[5]. Similar to human disease, genetic variation in gene regulatory elements can have a significant effect on drug response. Notably, 96.4% of genetic polymorphisms identified in GWAS of pharmacogenomic traits were in non-coding regions[6]. High-throughput and massively parallel methods were described to decode and characterize the impact of these variants[7].

BioBank and Electronic Health Records in Pharmacogenomics Research (Low, Tamari, Wu)

Electronic health record (EHR) and population biobanks offer enormous opportunities for pharmacogenomics research. Notably, the PGRN-RIKEN collaboration has exploited the EHR and biobanks to discover genetic variants that underlie a myriad of drug response phenotypes. At this meeting, a PGRN investigator from Harvard Medical School presented recent work on the genetic determinants of response to inhaled corticosteroids using large patient populations with asthma[8]. These patients were identified from the EHR and biobanks available from BioVU (https://victr.vanderbilt.edu/pub/biovu/), Marshfield Clinic (http://www.marshfieldresearch.org/chg/pmrp), and Research Program on Genes, Environment and Health (RPGEH) (https://rpgehportal.kaiser.org). In addition, we heard from RIKEN investigators about the BioBank Japan (https://biobankjp.org/english/index.html), a large resource where many discoveries have been made by investigators at RIKEN and their international collaborators. At this meeting, two speakers from RIKEN Institute presented their research using BioBank Japan for discovery of drug-induced toxicity[9] and to discover new loci for various allergies[10].

Summary

Despite the oftentimes tighter and clinically actionable phenotype, GWAS of drug response phenotypes lag behind GWAS of human disease and biological traits in terms of the number of published studies, the sample sizes, and the population diversity of the cohorts. Challenges remain in pharmacogenomics research to identify larger and more diverse cohorts, and/or more precise endophenotypes, to increase the power to make discoveries and to replicate findings. However, because drug targets and pathways are frequently understood, pharmacogenomics research can exploit this knowledge to validate findings from GWAS and to identify new mechanisms for therapeutic and adverse drug reactions and therapeutic

optimization. The PGRN-RIKEN collaboration continues to be among the most impactful international consortia for discovering the genetic variants that underlie drug response.

Investigators and trainees who attended the 2016 PGRN-RIKEN Meeting

Nadav Ahituv (University of California San Francisco), Deanna Brackman (University of California San Francisco), M. Eileen Dolan (University of Chicago), Jessica Enogieru (University of California San Francisco), Eric Jorgenson (Kaiser Permanente Division of Research), Koya Fukunaga (RIKEN IMS), Yoichi Furukawa (RIKEN IMS), Kathleen M. Giacomini (University of California San Francisco), Monique M. Hedderson (Kaiser Permanente Division of Research), Keiko Hikino (University of Chicago), Federico Innocenti (UNC Chapel Hill), Yoichiro Kamatani (RIKEN IMS), Jason H. Karnes (University of Arizona), Deanna L. Kroetz (UCSF), Michiaki Kubo (RIKEN IMS), Lawrence Lin (University of California San Francisco), Geoffrey Liu (Princess Margaret Cancer Center), Siew-Kee Low (RIKEN IMS), Yukihide Momozawa (RIKEN IMS), Danielle Mueller (Centre for Addiction and Mental Health & University of Toronto), Taisei Mushiroda (RIKEN IMS), Erika Nurmi (University of California Los Angeles), Kouros Owzar (Duke University), Sara Rashkin (University of California San Francisco), Mark J. Ratain (University of Chicago), Mayumi Tamari (RIKEN IMS), Tsunoda Tatsuhiko (RIKEN IMS), Rachel F. Tyndale (University of Toronto), Liewei Wang (Mayo Clinic), Richard M. Weinshilboum (Mayo Clinic), John S. Witte (University of California San Francisco), Ann Chen Wu (Harvard Medical School), Sook Wah Yee (University of California San Francisco).

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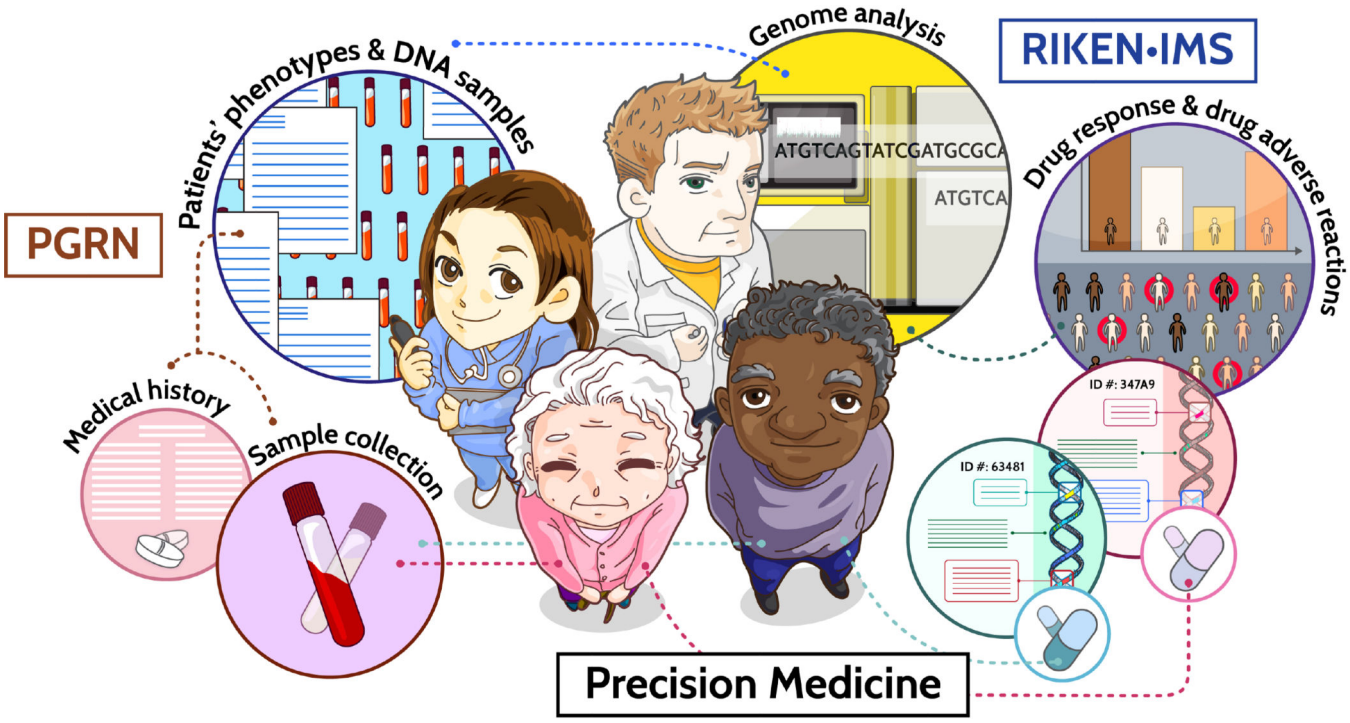

Figure 1. An infographic of the NIH Pharmacogenomics Research Network-RIKEN (PGRN-RIKEN) Collaboration

The website describing the collaboration can be found at http://www.pgrn.org/pgrn-riken.html

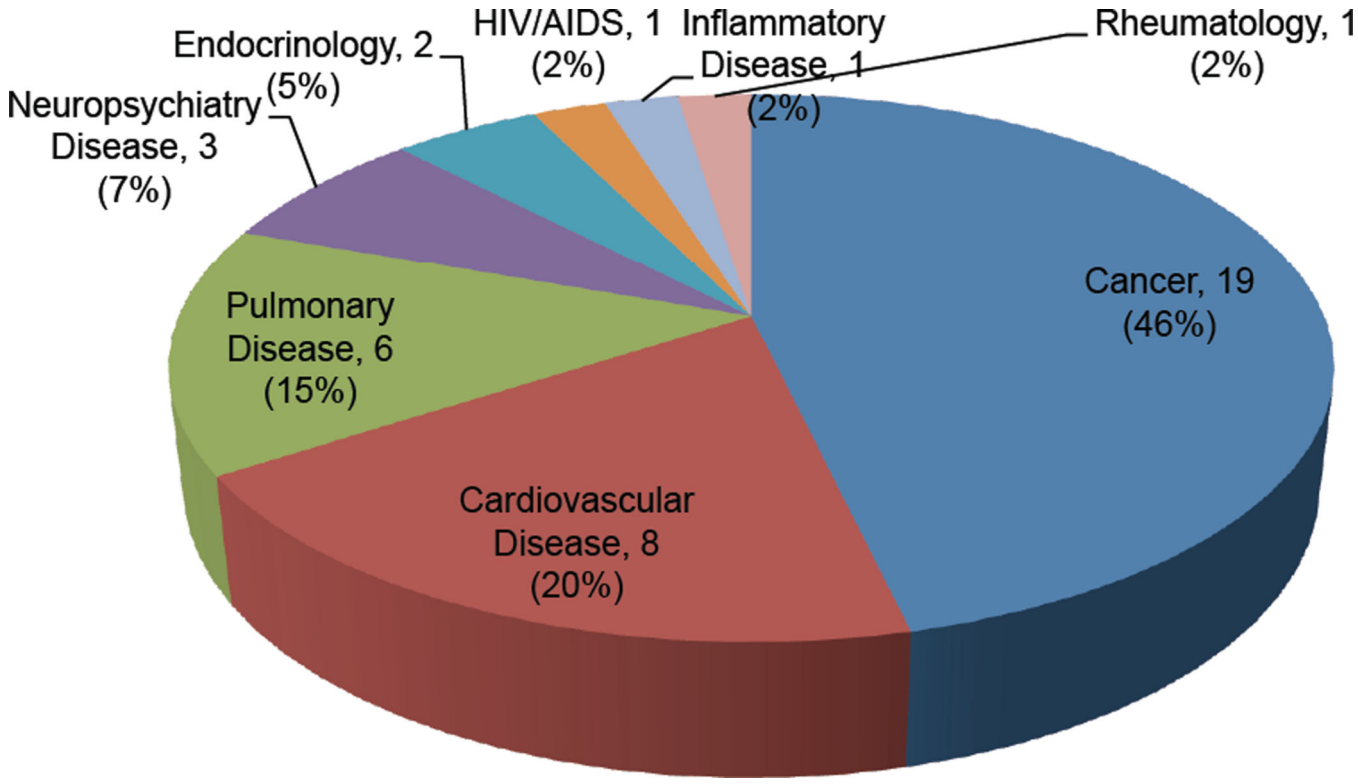

Figure 2. Eight study areas of PGRN-RIKEN Collaborative studies

A total of 41 studies were initiated through this international collaboration. Among the studies, 37 were genomewide genotyping and 4 were sequencing studies of top locus/candidate genes.