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COMMENTARY

Unveiling the Genetic Architecture of Human Disease for Precision Medicine

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This Commentary highlights proceedings from the workshop titled "Unveiling the Genetic Architecture of Human Disease for Precision Medicine" at the 2018 American Society for Clinical Pharmacology and Therapeutics Annual Meeting (ASCPT) in Orlando, Florida. With an emphasis on genomics and pharmacogenomics, this session focused on use of human genetics to identify new drug targets, improving assessment of benefit and risk using pharmacogenomics studies, and importance of considering differences in allele frequency across racial/ethnic populations during drug development.

GENETIC STUDIES TO INFORM DRUG DISCOVERY AND EARLY DEVELOPMENT

Preclinical animal models have traditionally been used to identify new drug targets, but the effectiveness of this strategy has come under scrutiny as costs for research and development increase. The poor predictive value of these preclinical models has also contributed to the rise of late-stage drug failures. Human genetic and pharmacogenomic studies have increasingly become a formidable resource for drug target discovery, for identification of drug targets and biomarkers, and for establishing causal relationships between drug target perturbation and physiological outcomes. Human genetic studies represent "experiments of nature" and can be exploited to discover new drug targets. Now standard approaches in human genetics can be leveraged to interrogate these experiments of nature and to advance drug development and biomarker identification. For instance, the discovery of proprotein convertase subtilisin/kexin type 9 (PCSK9) gene mutations led to the development of PCSK9 inhibitors. Genome-wide association studies (GWAS) have enabled large-scale identification of drug targets as well as offered mechanistic insights into disease biology. Phenome-wide association studies (PheWAS) are an effective strategy to uncover pleiotropic effects of genomic variation, to identify new indications for existing drugs, and to predict potential drug safety issues.[1,2] Mendelian randomization can establish causality between biomarkers and clinical outcomes and may be considered "nature's randomized controlled trial."[3] The growing availability of population-based cohorts makes these approaches increasingly accessible and powerful. However, both old and new challenges must be met to implement population-based approaches for drug discovery and development on such a large scale, including harmonization of phenotype definitions and replication of results.

These approaches have generated much insight into causal human biology. It is this understanding of human biology on which drug target selection should be primarily based (rather than simply relying on animal model data). Integrative approaches are still needed that leverage emerging technologies to link genetic variation with biological pathway, disease, and drug databases. After causal relationships are established, the genomic mechanisms still need to be matched to appropriate therapeutic modalities (e.g., small molecules, biologics, and antisense oligonucleotides) to deliver effective treatment.

One of the biggest challenges in drug discovery and development is matching therapeutic modality with underlying molecular mechanism of action. A limitation with conventional therapeutic modalities (i.e., small molecules and biologics) is that they are likely to target ≈10% of protein-coding genes. Newer therapeutic modalities, such as antisense oligonucleotides and clustered regularly interspaced short palindromic repeats (CRISPR), can target more of the genome that is currently considered to be "undruggable." A disciplined and rational approach to drug discovery and precision medicine can be achieved by integrating multi–omic-level data to uncover the genetic architecture of human disease.[3]

MUTATIONS IN SOLUTE CARRIER SUPERFAMILY TRANSPORTERS ARE CAUSAL FOR HUMAN DISEASE

The solute carrier (SLC) transporters play a role in normal physiological process by transporting several substrates (including nutrients, xenobiotics, and drugs) across biological membranes. This superfamily of transporters includes >395 membrane-bound proteins classified into 52 families based on sequence homology and functional role. The SLC transporter superfamily plays an important role in human diseases: 103 of the SLC transporters have mutations that are causal for mendelian disease, and many of the SLC

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transporters are highly associated with common diseases in many studies using GWAS[4].

Solute carrier family 2 member 2 (*SLC2A2*), an important liver glucose transporter, was identified as a determinant of metformin-induced reduction in hemoglobin A1c (HbA1c) through GWAS.[5] In contrast to common variants in *SLC2A2*, rare variants in this gene are the cause of a rare disease, Fanconi-Bickel syndrome (FBS). FBS patients with these loss-of-function variants have a range of less severe to more severe phenotypes associated with glycogen storage in the liver. This example highlights the differences in the impact of different *SLC2A2* variants on glucose homeostasis, and how human genetic studies can offer better insights into understanding human diseases and traits as well as pharmacological responses.

In contrast to SLC2A2, which has narrow substrate specificity, solute carrier family 22 member 1 (SLC22A1; also known as OCT1) is an organic cation transporter that is highly expressed in the liver and facilitates the transport of many prescription drugs and xenobiotics, such as metformin, tropisetron, morphine, and thiamine (vitamin B1). *SLC22A1* is highly polymorphic, and in fact, there are many common and reduced function missense variants in *SLC22A1* compared with its orthologs (*SLC22A2* and *SLC22A3*). These *SLC22A1* missense variants are associated with pharmacokinetics (PK) and pharmacodynamics (PD) of several drugs, including morphine and metformin. Interestingly, multiple human GWAS have shown that functional variants in *SLC22A1* are associated with high total and low-density lipoprotein (LDL) cholesterol levels, although the mechanism was unknown (GWAS Catalog, https://www.ebi.ac.uk/gwas). Recent studies by Liang *et al.* demonstrated the critical role of *SLC22A1* in modulating lipid levels and other metabolic traits through effects on hepatic thiamine contents.[6] Overall, GWAS revealed an association between variation in SLC transporters and various traits. Importantly, mechanistic studies provide an insight into the molecular mechanisms underlying the transport role of the SLC with the disease.

RACIAL/ETHNIC AND GENETIC DIFFERENCES IN DRUG EXPOSURE AND RESPONSE

Of the myriad of intrinsic and extrinsic factors that can lead to interindividual variability in drug exposure and response,[7] genetics is an important intrinsic factor that can have profound impact on both the exposure and response to the drug. Biomarkers and genetic factors are now routinely included in the therapeutic product labeling approved by the US Food and Drug Administration (FDA),[8] with >269 gene–drug pairs, including 207 unique drugs and 63 unique biomarkers included in the labeling as of December 2017. Of these 133 are considered actionable, i.e., genotype or phenotype information was listed in the Boxed Warning, Indications and Usage, Dosage and Administration, or Warnings and Precautions section of the labeling, and the biomarker is tied to explicit recommendations on dosing or use.[8] Personalized/precision medicine approvals have increased over the past several years; several of these precision medicines are being coapproved with a companion diagnostic (and increasing, complementary diagnostics) to identify the right target patient population.

Race/ethnicity is an important intrinsic factor that should be considered during drug development. About one in five new drugs approved by the FDA between 2008 and 2013 reported some difference in exposure and/or response across racial/ethnic groups in PK, safety, efficacy, dose change, and pharmacogenetics.[9] In some instances, this also translated into population-specific prescribing recommendations as well as needing postmarketing studies.[9] Racial/ethnic differences in the frequencies of functional variants are common for some important pharmacogenes that are involved in drug metabolism and transport (e.g., *CYP2D6*, *CYP2C9*, and *CYP2C19*), drug target or pathway (e.g., *EGFR*), and immunological reactions (e.g., *HLA-B*). For example, product labeling of carbamazepine, an anticonvulsant, includes a boxed warning for serious dermatologic reactions and the *HLA-B*15:02* allele. The *HLA-B*15:02* allele is highly associated with the outcome of carbamazepine-induced Stevens–Johnson syndrome and toxic epidermal necrolysis. The risk in some Asian countries is estimated to be about 10 times higher than in countries with mainly white populations. The labeling recommends that the patients with ancestry in genetically at-risk populations should be screened for the presence of *HLA-B*15:02* prior to initiating treatment.

Racial/ethnic differences in frequencies of certain genetic mutations can also affect clinical trial enrollment patterns. Development of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI), such as gefitinib, erlotinib, and afatinib for the treatment of non-small cell lung cancer (NSCLC), led to the recognition that the presence of EGFR TKI–sensitizing mutations in tumors can drive benefit to these therapies. These mutations are present in ≈10% of patients in North America and Western Europe and up to 50% of patients of East Asian descent, thus leading to higher enrollment of Asians subsequently during drug development to increase screening efficiency.

However, despite the recognition of the fact that the frequency of important pharmacogenetic variants may be different across racial/ethnic populations and an increase in the number of countries hosting clinical trials, the patient population enrolled in the clinical trials remains predominantly white, with limited racial/ethnic diversity.

SUMMARY

In summary, this workshop explored the role, impact, and contribution of human genetics in the discovery, development, regulation, and use of precision medicines. Human genetics can inform drug discovery and development via identifying targets to pursue, matching modality with mechanism, guiding biomarker identification, and identifying appropriate populations and indications for clinical trials (**Figure 1**). Pharmacogenomic factors can also affect the risk/benefit profile of a therapeutic product. Consequently, pharmacogenomic evaluations may be particularly valuable for drugs that exhibit highly variable PK, safety, or efficacy profiles; ideally, such evaluations should begin early in drug development, especially if the drug is a substrate or target of the gene. During drug development (and particularly for

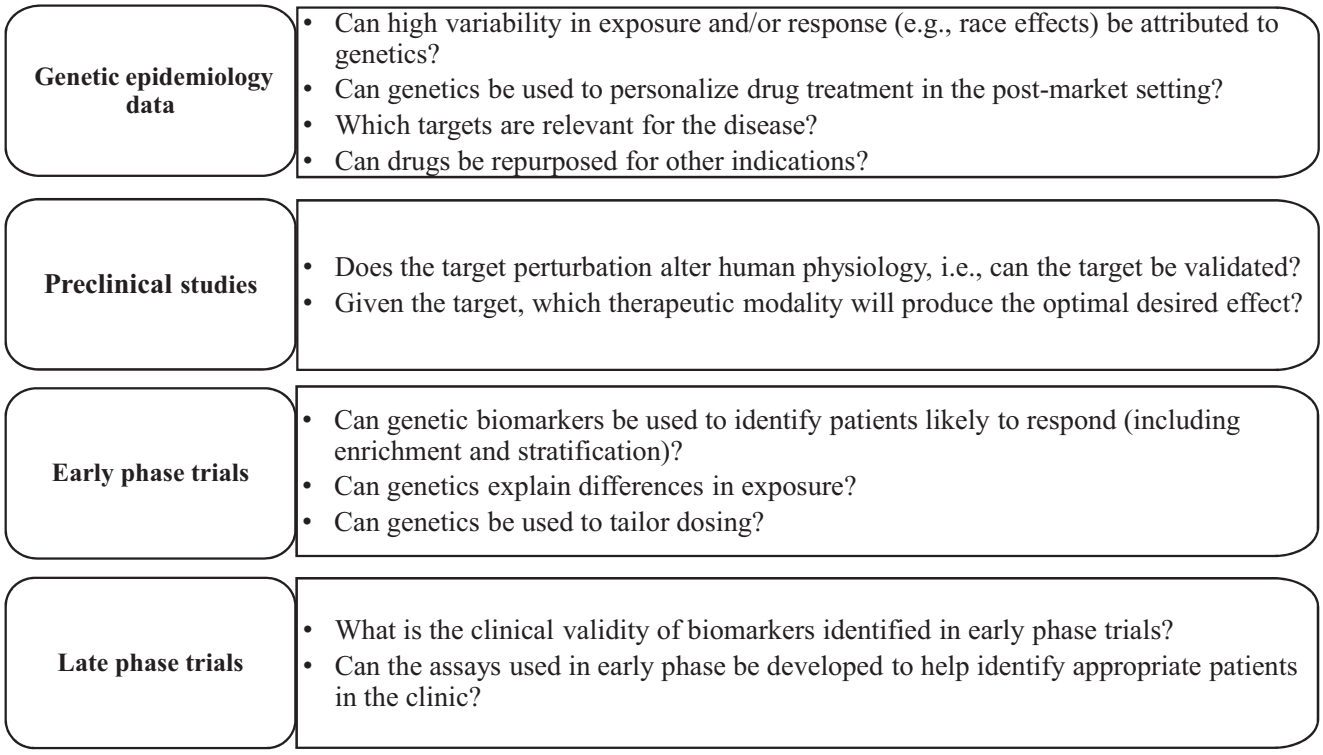

Figure 1 Leveraging human genetics and pharmacogenomics in the development of precision medicines.

precision medicines), there is a continued need to consider genetics as well as racial/ethnic differences in the frequencies of genetic factors. The ultimate goal is to leverage advances in human genetics using both the existing technologies and emerging tools to uncover the architecture of human diseases, to personalize drug treatment, and to facilitate translation of discoveries into clinical care.

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