CONCEPT CLEARANCE FOR RFA

NHGRI Advisory Council, May 2008

Genome-wide Association Studies of Treatment Response in Randomized Clinical Trials

Purpose

Staff seeks Council clearance for two RFAs to support genome-wide association (GWA) studies in randomized controlled clinical trials to identify genetic variants associated with response to treatments for conditions of clinical or public health significance. One RFA will solicit applications for 3-5 Study Investigators and the other will support a data and analysis Coordinating Center. The goal of this U01 program is to utilize existing clinical trial data and sample resources to: 1) identify genetic variants that influence an individual's response to treatment; 2) determine whether specific treatments are more or less effective in groups defined by genotype; and 3) develop and disseminate innovative methods for adding genome-wide technologies to randomized clinical trials and interpreting the results in the context of a randomized treatment assignment.

Background

Patients are known to vary considerably in response to drug therapy and other interventions, both in magnitude of treatment effect and in risk of adverse events; much of this variation has been hypothesized to have a genetic basis. Growing evidence supporting this hypothesis includes identification of variants in *CYP2C9* and *VKORC1* that explain roughly 40% of variation in warfarin dosage requirements, variants in *ADRβ2* that are strongly associated with response to bronchodilators in asthma, and variants in *GRIK4* and *HTR2A* associated with response to citalopram treatment for depression. Variants in *TCF7L2*, *KCNJ11*, and *PPARγ* have been investigated in relation to the impact of lifestyle modifications on incidence of diabetes. Adverse drug reactions have also been related to genetic variation, including variants in *TPMT* and treatment with purine antimetabolites, *UGT1A1* and irinotecan therapy, and *HLA-B*5701* and abacavir treatment.

Despite these initial successes, known variants generally explain a small proportion of the estimated genetic variability of response to many of these therapies. Identification of variants related to treatment response to date has largely relied on candidate gene studies, much as did research in the genetics of complex diseases before the advent of GWA studies. Studies of drug response have been slow to adopt the GWA approach, perhaps because pharmacologic mechanisms and pathways are likely to appear more clearly defined than pathophysiologic mechanisms of complex diseases, lending greater credence to the candidate gene approach. In addition, clinicians may feel that current clinical measures with which they are familiar will suffice to monitor drug response without the need for additional information on genetic variants. Early pharmacogenomic studies have also placed an understandable emphasis on severe adverse drug reactions, which are generally too uncommon to permit accrual of the large series of cases needed for GWA studies. In contrast, clinical improvement (or lack thereof) in response to treatment is a frequently occurring outcome in clinical trials, so that large numbers of responders

and non-responders can readily be collected. When treatment response can be assessed as a continuous trait, as is often the case, power of GWA studies is even greater.

Randomized clinical trials represent an outstanding opportunity for identifying genes related to treatment response due to their typically detailed characterization of response to treatment during the course of the trial, as well as their extensive baseline assessment of study eligibility prior to study entry. This wealth of data not only provides a variety of intermediate phenotypes and treatment responses that can be related to genomic variation, but also often includes non-genetic exposures such as other medications, co-existing illnesses, lifestyle factors, and other environmental influences to permit evaluation of factors modifying any gene-treatment associations identified. Randomization provides the opportunity to evaluate genetic influences on treatment response in a setting where confounding of treatment effect by indication is eliminated—indications for treatment are similar (or any differences are due to chance alone) regardless of treatment assignment. Randomization also allows assessment of response in subgroups defined by genotype, for evaluation of gene-treatment interactions, as has been done in the Diabetes Prevention Program with variants in *TCF7L2*, *KCNJ11*, and *PPARγ*. GWA studies also provide a rich context for developing analytical methods in the setting of a randomly-assigned environmental exposure (the randomized therapy) and its potential interactions. Clinical trials have lagged behind other population-based designs such as case-control and cohort studies in adopting genome-wide technologies, and analysis and release of genomic data are often complicated by the need for masking of treatment assignment until the trial is completed. Addition of genome wide methods to completed clinical trials will facilitate both the application of genomic technologies to population studies and the development of research resources that are the core goals of NHGRI's population genomics efforts.

Research scope and objectives

This program will support multiple investigative groups to conduct GWA studies on existing DNA samples and data from roughly 2,000 participants per treatment arm in randomized controlled clinical trials. For the purposes of this program, a treatment is defined as an intervention, whether involving drug, dietary, and/or lifestyle modification, that aims to reduce morbidity and/or prevent disease. Each Study Investigator will be supported to provide high-quality DNA to an NHGRI-designated genotyping facility for GWA genotyping, and to submit extensive phenotype and exposure data to the program's Coordinating Center and dbGaP for distribution through open and controlled processes in accordance with NIH-wide GWAS policies. Awardees will be supported to analyze genotype-treatment associations and disseminate the results to the scientific community. They will also work collaboratively with the program's Coordinating Center, NHGRI, and each other to develop methods for analyzing gene-treatment associations and their modifiers, incorporating genomic studies into clinical trials, and disseminating data and results. Although it is expected that data analysis and dissemination must await unmasking of treatment assignment, and hence completion of the clinical trial, applicants who can demonstrate that analysis and dissemination can proceed in an ongoing trial without threatening the trial's integrity will be eligible to apply. Data and samples must be ready for submission within nine months of award, and for unmasked analysis within 12 months of award.

Even for treatments that show a clear population-wide benefit, particular population subgroups may exhibit differences in treatment benefits or harms. The highest programmatic priority will be given to trials that include participants representative of the U.S. population, address conditions or treatments of public health importance, and provide extensive phenotypic and exposure information. Availability of suitable replication populations will also be an important consideration, though replication in an adequately-sized randomized trial, testing the same interventions in the same populations, may be difficult to achieve. Applicants may propose other approaches with suitable justification, such as replication of gene-treatment associations in observational studies. Investigators without replication components identified and available at the time of application should clearly document relevant ongoing collaborations and describe a plan to establish additional collaborations as needed to permit replication of findings.

The Coordinating Center RFA will support a multidisciplinary group of statistical geneticists, clinical trials, epidemiologists, and bioinformaticians who will coordinate receipt and harmonization (where appropriate) of phenotype and exposure data for submission to dbGaP, assessment of genotyping data quality, and analysis of genotype-treatment associations as needed. They will also manage the administrative and logistical aspects of the collaborative program. The precise balance of Coordinating Center activities will depend on the experience and capacity of the Study Investigators, so applicants will need to demonstrate a range of available capabilities and flexibility in utilizing them as needed.

The Study Investigators, Coordinating Center, and NHGRI will meet as a Steering Committee three times a year, and by conference call on an ongoing basis, to identify and address common genotyping and analytic issues and explore opportunities for synergy among studies. Development and dissemination of methods and best practices for incorporating genomic studies in clinical trials, including approaches for establishing needed infrastructure for genomic research, will be another important product of this collaborative program.

Mechanism of support

This funding opportunity will use the NIH U01 Cooperative Agreement award mechanism. Study Investigator and Coordinating Center applicants will be able to request up to 3 years of support.

Funds available

NHGRI will commit approximately $21 million in total costs over a 3-year period, to fund one Coordinating Center (approximately $4 million) and 3-5 Study investigators (approximately $17 million, including $10 million in genotyping costs). Co-funding support from other NIH ICs is proposed and will be solicited.