

GENETIC ARCHITECTURE OF COMPLEX PHENOTYPES

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National Institute of Environmental Health Sciences
National Institute of Arthritis and Musculoskeletal and Skin Diseases
National Institute on Aging
National Institute of Mental Health
National Institute of Drug Abuse
National Institute on Alcohol Abuse and Alcoholism
National Institute of Child Health and Human Development
National Human Genome Research Institute
National Heart, Lung, and Blood Institute

PURPOSE

The purpose of this initiative is to support new studies on the architecture of complex phenotypes, including research using human and model systems as well as research using theoretical approaches. The studies targeted by this program announcement are expected to expand our understanding of the roles of genetic and environmental variation and their interactions in causing phenotypic variation in populations; increase the quantity and quality of population-based data; lead to development of mathematical and statistical tools for analyzing measured genotype data; lead to improvements in study design; and create biologically relevant models for understanding the origins, roles and implications of genetic variation in causing variation in phenotypes.

HEALTHY PEOPLE 2000

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2000," a PHS-led national activity for setting priority areas. This PA, Genetic Architecture of Complex Phenotypes, is related to several priority areas. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0 or Summary Report: Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402-9325 (telephone 202-512-1800).

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign, for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Foreign institutions are not eligible for program projects (P01) grants. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as principal investigators.

MECHANISM OF SUPPORT

This Program Announcement will use the National Institutes of Health (NIH) research project grant (R01) and program project grant (P01) mechanisms. Supplements to existing NIH grants will also be considered. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant.

Applications requesting direct costs of \$500,000 in any one year must obtain written agreement from the assigned institute that the application will be accepted for consideration of award, in accordance with NIH policy, which is available at <http://www.nih.gov/grants/guide/notice-files/not98-030.html>.

RESEARCH OBJECTIVES

Complex phenotypes are those that exhibit familial clustering, which suggests at least some genetic component, but they do not occur in Mendelian proportions in pedigrees. Such phenotypes may have relatively simple underlying genetics, but their transmission appears complex because of its context, including interactions with other loci and with the environment. Alternatively, complex phenotypes may have multiple genetic and environmental causes. Most chronic, common diseases are complex by this definition. Complex phenotypes may be continuous in distribution, like height or blood pressure, or they may be dichotomous, like affected and not affected. The complexity arises from the fact that many genetic and environmental factors may interact with each other in unpredictable ways, such that the association between the phenotype and any single factor taken by itself may be imperceptible. Nonlinear interactions, including epistasis and genotype by environment interactions, mean that the expression of the phenotype may not accurately predicted from knowledge of the individual effects of each of the component factors considered alone, no matter how well understood the separate components may be.

The term genetic architecture is used to encompass the full range of genetic effects on a trait, with emphasis on the context dependence of the expression of those genes in manifesting a phenotype. A full cataloging of the genetic architecture of complex phenotypes consists of a description of all of the genetic and environmental factors that affect the phenotype, along with the magnitude of their individual effects and the magnitudes of interactions among the factors. It is, in principle, possible to describe the genetic components in terms of Mendelian segregation and location along a genetic map. Environmental factors are, in general, much less easily partitioned into separate factors whose individual effects and interactions can be sorted out.

Consideration of the evolutionary and developmental context of complex phenotypes is critical, since these approaches may yield important information about how the architecture of a phenotype arises. Other scientific disciplines, including mathematics, biochemistry, ecology, molecular biology, and physics, may also make important contributions to understanding genetic architecture.

Genetic architecture is less a fundamental biological property of the phenotype than a characteristic of a phenotype in a particular population. The genetic architecture is a moving target that changes according to gene and genotype frequencies, the distributions of environmental factors, and such biological properties as age and sex. The implication of the population dependence is that the predominant genetic factors contributing to a complex phenotype may seem to differ from population to population. This is one explanation for the apparent heterogeneity sometimes found in the results of genetic linkage studies in different populations. Alternative explanations include insufficient statistical power in the linkage tests and the possibility that superficially identical complex phenotypes in different populations may actually have different biological causes. It is not now possible, in most cases, to differentiate among these various explanations.

Strictly speaking, it may not be possible to fully quantify the complete genetic architecture of a complex trait. One is limited by statistical power to identify only factors and interactions having relatively large effects. In an ideal case, when the factors are not numerous, when their main effects are quite large and their interaction effects quite small, and when interpopulation heterogeneity is minimal, very rapid progress in characterizing the underlying architecture of a phenotype can be made. An important goal is to be able to rapidly identify phenotypes whose underlying genetics is more tractable from those having much more complex etiology.

Technological advances are, in part, responsible for the current excitement over the prospects for advances in understanding complex phenotypes. Large amounts of data on DNA sequences and variation are now available, and new technologies will soon make it easy and inexpensive to produce many times more. DNA chips and other technologies for scoring enormous numbers of single nucleotide polymorphisms (SNPs) throughout the genome will greatly accelerate application of genomic scans. Our capacity for synthesizing, analyzing, and interpreting this amount of genomic data is currently inadequate. The challenges are conceptual (for example, how to identify nonlinear interactions or how to optimize computational algorithms), clinical (how to define phenotypes), and epidemiological (how to sample in such a way as to minimize spurious associations due to population structure and population history while maximizing the power to detect biologically significant associations).

This program announcement restates the interest of several components of the National Institutes of Health in studies of the underlying causes and architecture of complex phenotypes. It is motivated by the amount and complexity of data that are being generated and by the understanding that complex phenotypes involve many genes that evolve in a variety of environments. The areas listed below exemplify some research efforts appropriate to this program announcement.

Data Collection:

Although in many fields, there is a preference for hypothesis-driven research, studies on genetic architecture suffer from a paucity of high-quality, population-based data. This program announcement encourages efforts to collect useful information that will support the ultimate goals of the program announcement. These efforts include the following:

- o Organization of DNA sequence variation in populations and subpopulations with the goal of understanding the causal forces that shape that organization
- o Structure of variation across the genome, populations, and phylogenies
- o Effects of admixture, population history, recombination, mutation, population structure, selection, and drift on the organization of variation
- o Collection and analysis of both new and existing data
- o Studies of the relationship of genotypic and phenotypic variation
- o Causes and implications of genotype by environment interactions and genotype by sex interactions
- o Genetic, population, environmental, and evolutionary dynamics that are responsible for observed levels of genotypic and phenotypic variation
- o Determination of the extent to which genetic architecture is shared across populations and between species

Data Analysis:

Tools for analyzing and interpreting data on the architecture of complex phenotypes should be developed in the context of real biological information. The focus is on approaches that may be applied to a variety of biological data. Areas of particular interest include the following:

Research on study design, including comparisons of different strategies for studying complex phenotypes

- o Implications and appropriate uses of different sampling strategies
- o Implications of various methods of ascertainment
- o Implications of subdividing or pooling samples

Development of statistical and analytical tools

- o Tools that will allow scientists to make inferences about architecture of complex phenotypes from genomic data
- o Tools to allow the integration of various kinds of relevant data such as linkage, linkage disequilibrium, and sequence data
- o Statistical tools for analyzing data to discover genotypic and phenotypic relationships
- o Analytical tools to discover patterns of genotypic variation and their roles in conferring phenotype

Taking into account the future scale of genotype data, construction of meaningful tests of relationships between genotypic and phenotypic data

- o Determining the patterns of haplotype variation that will direct the search for sequence variation that is causal to phenotype
- o Incorporation of phase-known and phase-unknown haplotype data
- o Incorporation of data from new technologies
- o Development of robust methods that are compatible with real data (missing or incomplete data, typing errors, experimental errors)
- o Incorporation of epistasis tests for multiple locus interaction and linkage disequilibrium
- o Robust methods to detect errors in phenotyping, classification of phenotypes, or redefinitions of phenotypes
- o Methods to interpret observed relationships

Models:

Models should be based on empirical information which includes such biological realities as epistasis, crossing over, mutation, gene conversion, interference, population history and

subdivision, selective sweeps, background selection, and so on. We need to learn more about how these forces shape the relationship between genotype and phenotype, and how knowledge of these effects can be used to investigate genetic architecture empirically. Both simulation studies and analytic formulations are appropriate. Areas of interest include the following:

Models to help optimize research study design in a variety of human and model populations

- o Sampling schemes and theory for determining genotype/phenotype relationships
- o Use of special populations, such as admixed, founder, and isolates, to study genotype/phenotype relationships
- o Models of non-human organisms with the goal of helping investigators select the best model for specific research questions
- o Evolutionary history of the genetic architecture of complex traits as applied to research designs
- o Patterns of linkage disequilibrium and variation in admixed populations, given variability in population history, including relationships of gene conversion and crossing over with admixture
- o Gene genealogies of underlying causal genes and how selection on a complex phenotype may leave a signature on patterns of extant genetic variation

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification is provided that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103 43).

All investigators proposing research involving human subjects should read the "NIH Guidelines For Inclusion of Women and Minorities as Subjects in Clinical Research," which have been published in the Federal Register of March 28, 1994 (FR 59 14508-14513) and in the NIH Guide for Grants and Contracts, Volume 23, Number 11, March 18, 1994.

Investigators also may obtain copies of the policy from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

NIH POLICY AND GUIDELINES ON THE INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them. This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects" that was published in the NIH Guide for Grants and Contracts, March 6, 1998, and is available at the following URL address: <http://www.nih.gov/grants/guide/notice-files/not98-024.html>

APPLICATION PROCEDURES

Applications are to be submitted on the grant application form PHS 398 (rev.5/95) and will be accepted at the standard application deadlines as indicated in the application kit. Applications kits are available at most institutional offices of sponsored research and may be obtained from the Division of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone 301/435-0714, email: grantsinfo@nih.gov.

The title and number of this program announcement must be typed in Section 2 on the face page of the application.

The completed original application and five legible copies must be sent or delivered to:

CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040 - MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817 (for express/courier service)

REVIEW CONSIDERATIONS

Applications will be assigned on the basis of established PHS referral guidelines. Applications will be reviewed for scientific and technical merit by an appropriate initial review group. As part of the initial merit review, a process will be used by the initial review group in which applications will be determined to be competitive or non-competitive based on their scientific merit relative to other

applications received in response to the PA. Applications judged to be competitive will be discussed and be assigned a priority score.

Applications determined to be non-competitive will be withdrawn from further consideration and the Principal Investigator and the official signing for the applicant organization will be notified.

Following the initial scientific- technical review, the applications will receive a second level review by an appropriate National Advisory Council.

Review Criteria

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written review, comments on the following aspects of the application will be made in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in the assignment of the overall score.

o Significance. Does the proposal address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

o Approach. Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate? Are there appropriate interdisciplinary components? Does the applicant acknowledge potential problem areas and consider alternative tactics?

o Innovation. Does the project employ novel concepts, approaches or method? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

o Investigator. Is the investigator appropriately trained and well suited for the project? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any) on the project?

o Environment. Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment? Is there evidence of institutional support?

The initial review group will also examine the provisions for the protection of human and animal subjects and the safety of the research environment as well as the adequacy of plans to include

both genders, minorities and their subgroups, and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.

AWARD CRITERIA

Applications will compete with all other approved applications for available funds. The following will be considered in making funding decisions:

- o the quality of the proposed project as determined by peer review
- o program priority
- o availability of funds.

INQUIRIES

Inquiries are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

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AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance Nos.93.821, 93.859, 93.862, 93.113, 93.846, 93.866, 93.242, 93.273, 93.279, 93.865, 93.172, and 93.837. Awards are made under authorization of the Public Health Service Act, as amended and administered under PHS grants policies and Federal Regulations 42 CFR 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, and portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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