

## CONCEPT CLEARANCE

### Request for Applications (RFA)

#### **Ethical, Legal, and Social Implications (ELSI) of Studies of Recent Positive Natural Selection in the Human Genome**

##### *Background and Purpose*

Positive natural selection--the phenomenon that accounts for the increase in the prevalence of advantageous traits in a population--has played an important role in our development as a species. When populations are subject to different environmental, disease, or cultural pressures, natural selection may change the frequencies of alleles in one population relative to another. Large differences in allele frequencies between populations may thus signal places in the genome that have undergone selection, in some cases very recently. Other signals of recent positive selection include long haplotypes and reduced allelic variation in the regions around the selected variants.

The characterization of signatures of recent positive selection in genes that are of adaptive significance in humans can have great medical relevance, by helping to identify functionally significant variants that play a role in health and disease. However, research on recent positive selection in the human genome is fraught with methodological challenges and has significant ethical and social implications. The findings of studies that attribute differences in allele frequencies to recent positive natural selection may challenge the way we think about the meaning of human differences. Where the frequencies differ substantially between populations (as defined by ancestral geography), these findings may affect the way we think about differences (both real and perceived) between people from various racial and ethnic groups.

The goal of this RFA is to encourage more focused and systematic study of the ethical and social issues likely to be raised by the increasing body of research on the role of recent positive natural selection in shaping human traits and in explaining differences within and among human populations.

##### *Research Scope*

This initiative will welcome applications that address a wide range of topics regarding recent positive natural selection in the human genome. The focus of the RFA will be on issues that arise from studies of *recent* selection in modern humans—not on issues that arise from studies of evolution more generally or of the relationships between humans and other species, such as chimpanzees. Examples of appropriate questions include, but are not limited to:

- How similar or different are the ethical, legal, and social implications of studies that hypothesize recent positive natural selection in humans, depending on such factors as:

- whether the trait claimed to be under selection varies *between* populations (defined in terms of ancestral geography) or *within* populations (i.e., among individuals within populations), or both
- whether the trait claimed to be under selection relates to the physical environment (e.g., ability to tolerate high altitudes), the disease environment (e.g., resistance to AIDS), the cultural environment (e.g., ability to drink milk in adulthood), or other types of environments
- whether the trait claimed to be under selection is associated with a selection tradeoff (e.g., CFTR heterozygotes being more resistant to typhus and tuberculosis but homozygotes having cystic fibrosis; hemoglobin AS heterozygotes being more resistant to malaria but SS homozygotes having sickle cell disease)
- whether the trait claimed to be under selection is seen as generally advantageous in all environments or as one that confers an advantage for people with some genotypes or in certain environments but not for others (e.g., individuals with thalassemia or G6PD deficiency)
- whether the trait claimed to be under selection is still under selection in a particular geographic area, versus not being under selection in a different geographic area (e.g., malaria resistance in places where malaria is common, versus thalassemia or sickle cell disease in places where malaria is uncommon)
- How do genetics and genomics researchers in studies that hypothesize recent positive natural selection in humans as an explanation for allele frequency differences (either within or between populations) design their studies? What steps could or should be taken to improve the design of these studies in the following areas?:
  - defining the populations under study
  - defining the phenotypes under study
  - accounting for the possible effects of demographic events other than natural selection (for example, population bottlenecks, drift)
  - accounting for the possible effects of non-genetic factors?
  - quantifying or otherwise operationalizing the selective forces hypothesized as an explanation for allele frequency differences
  - ascribing function to a particular gene when there may be several genes in a region showing signals of selection
- Should “community standards” be developed to help ensure that studies of recent positive natural selection in humans are appropriately designed and that conclusions are adequately supported by evidence? Should heightened standards of replication apply to such studies? What would be the advantages and disadvantages of adopting such standards?
- Are there particular characteristics of the social environment that may influence the propensity of genetics and genomics researchers to attribute allele frequency differences within or between populations to recent positive natural selection as opposed to other demographic events?

- How has the popular press historically reported on studies that purport to find evidence of recent positive natural selection in humans? Of studies that posit other explanations for individual or group allele frequency differences?
- How do members of the public understand stories in the press that suggest recent positive natural selection in humans as a possible explanation for individual or group allele frequency differences? How does their understanding of recent positive natural selection relate to their conceptions about the mutability or immutability of differences? About differences between racial and ethnic groups?
- How do members of the public understand the “Out of Africa” theory of human population history, and how does that relate to their views regarding the possible role of recent positive natural selection in humans in contributing to perceived differences between human populations?
- What are the general ethical obligations of each of the following to ensure that research on recent positive natural selection in humans is properly framed, designed, and interpreted, that the findings of such research are accurately and sensitively reported, and that the findings are appropriately used?:
  - genetics and genomics researchers
  - science reporters and the popular press
  - educators and policymakers
  - funding agencies (including the peer review process)

### ***Investigators***

Investigators from a variety of disciplines, including anthropology, sociology, psychology, history, political science, economics, philosophy, law, communications, science education, genomics, and genetics, are encouraged to apply. This area of research is inherently trans-disciplinary. Thus, applicants are strongly encouraged to include on their research teams, as key personnel, both individuals with expertise in ELSI research and individuals with expertise in genomics, genetics, or other relevant clinical or basic sciences. In making funding decisions, highest priority will be given to applicants who propose such trans-disciplinary teams. Applications from underrepresented minority investigators and investigators with disabilities are especially encouraged to apply.

### ***Mechanisms of Support***

This RFA will use the regular research grant (R01) award mechanism.

### ***Funds Available***

NHGRI will commit up to a total of \$1.5 million per year for each of three years for this initiative, to fund 3-5 R01 applications.