Research Grant 2024 Priority Areas

For the award cycle beginning April 1, 2024

Priority Areas

Priority will be given to proposed projects that use experimental or analytical approaches that complement ongoing efforts by the GREGoR Consortium. [Focus areas of each Research Center can be found here.](#) GREGoR samples span a wide spectrum of rare diseases, and we encourage proposals focused on a broad range of phenotypes, disease areas, and organ systems. *Note: Pre-submission inquiries, Letters of Intent (LOIs) and applications may be shared confidentially with members of the GREGoR Opportunity Fund Committee to review for fit and alignment with GREGoR goals.*

Proposals that are non-responsive (not eligible) for this funding announcement are described below:

1. Proposals to carry out routine diagnostic sequencing are not eligible.
2. Proposals that focus on common genetic variation or phenotyping of existing models without modeling new candidate genes/variants will be considered non-responsive.
3. Proposals to carry out sequencing and/or analysis of individuals whose samples are not part of a GREGoR center's study cohort are not eligible. Researchers or clinicians who would like to collaborate with GREGoR Research Centers on these types of projects can find [information here on ways to collaborate with the GREGoR Consortium](#) or can email the Consortium's Data Coordinating Center at <gregorconsortium@uw.edu>.
4. Functional validation or follow-up studies only applicable to a small set of genes are not eligible.

Priority research areas that are appropriate for this funding announcement include but are not limited to:

1. **Experimental approaches for functional validation or prioritization of GREGoR candidate genes and/or variants**
   a. The Consortium is currently using a number of methods to establish or refute the causality – and further biological understanding – of candidate genes and variants. Broadly, these include: generation of disease models, RNA-sequencing, saturation genome editing, metabolomics, epigenetic assays, splicing assays, and induced neuronal cell and induced cardiomyocyte phenotyping. Consortium-generated disease models principally involve CRISPR-generated human cell lines including iPS cells, induced neural lines, and induced cardiomyocytes, but also fly, mouse, and zebrafish organism models.

b. To supplement these largely "one-gene/variant-at-a-time" approaches, we are soliciting proposals that would test the functional effect of variants in >50 genes (or of >50 variants in a smaller number of genes) at a time – ideally in a single experiment.

c. Proposals should test variants that have been found in human patients, at least some of which would be variants identified by GREGoR as potentially causally impactful for rare disease (to be determined via discussion with the Consortium in the first quarter of the award) but may also include additional genes/variant candidates derived from other rare disease sources.

d. Successful proposals may overlap with the above approaches or those of other consortia, so long as there is novelty to the experimental design and/or set of genes/variants to which it is applied, as well as no overlapping funding.

e. Proposals that will be applied to noncoding, repetitive, or complex structural candidate variants will be given highest priority.

2. **New genomic technologies / molecular assays that can be applied to unsolved cases**

a. Projects to pilot the use of emerging or novel genomic technologies that could help resolve existing GREGoR samples that have remained unsolved after exhaustive sequencing and analysis (e.g. spatial sequencing, benchmarking experiments). Assays already run on many GREGoR samples include short read exome/genome sequencing (Illumina), RNA-seq, and long read (PacBio and Nanopore) genome sequencing, metabolomics and Optical Genome Mapping (Bionano platform). Available samples likely include banked DNA, banked RNA, frozen cells/tissue (in select cases), and patient-derived cell lines (in select cases).

b. If a new assay is being developed on non-GREGoR samples, proposals must demonstrate that the assay would also have utility for GREGoR cases (i.e. unsolved after genome sequencing at a minimum).

3. **User-friendly interfaces for interactive or batch annotation and interpretation of candidate variants in non-coding regions. Such an interface should provide tools and accompanying interpretation guidance (cutoff scores/ranks/etc.) that are easily utilized by a broad range of clinicians and researchers.**

a. High priorities include tools that can address:

i. Given genomic coordinates of a (typically non-coding) single nucleotide variant (SNV) or indel:

1. Does the variant add or remove a transcription factor binding site; is the predicted change in the transcription factor binding likely to have a large effect on gene regulation consistent with a monogenic cause of disease?

2. For which gene(s) is the variant predicted to decrease or increase expression, by how much, and in which tissues?

ii. Create a comprehensive set of annotations of predicted regulatory elements for specific tissues/developmental stages of interest for Mendelian conditions evaluated by GREGoR that could be used to identify candidate regions for novel/unsolved Mendelian phenotypes (e.g. developmental heart defect, cerebellar malformation, limb malformation, skin, immune system, malformation of reproductive organs, muscular dystrophy, cornea, neurodevelopmental conditions, and holoprosencephaly).

b. Tools may be:
i. Web portals for annotating small numbers of variants
ii. Command line executables applicable to genome-scale data (e.g. VCFs)

4. **Novel analytical approaches useful for analyzing GREGoR molecular data (these data include, but are not limited to: short-read DNA and RNA sequencing, long-read Nanopore and PacBio sequencing, methylation array and sequencing, metabolomics, optical genome mapping)**

a. Highly desirable analytical approaches include:
i. Head-to-head comparisons of available bioinformatics tools for calling/discovery or pathogenicity prediction.
ii. Development or piloting of new computational tools for variant filtration/analysis. This is especially needed for data types newly/recently applied for rare disease research such as RNA-Seq data and methylation data from long read (Nanopore or PacBio) sequencing.
iii. Bioinformatics tools that integrate analysis of two or more types of data. For instance, multi-omic approaches that enable coordinated variant prioritization across short-read DNA and RNA sequencing or across short-read DNA and long read sequencing.

5. **Development of software that increases the utility of the GREGoR Combined Consortium Dataset for rare disease research by providing summary/aggregate genotype and phenotype information**

a. The Consortium Data is hosted on the NHGRI AnVIL platform and is structured to conform with the GREGoR Consortium Data Model. Proposed software should leverage the GREGoR Data Model which is designed to integrate family, clinical and phenotype information with experimental metadata and quality control information.
b. Highly desirable are applications that propose software compatible with or executable on AnVIL and that enable sophisticated and semantically integrated queries (e.g. cohort building or case matching based on phenotypic similarity), and analysis across variant, gene, disease, and phenotype data as structured in the GREGoR Consortium Data Model.
c. Proposed software must be open source, well documented, and freely available for use or modification by others.