Call 2016, February: 'GenOmics of rare diseases'

The French Foundation for rare diseases (Fondation maladies rares) is pleased to launch its new call for research projects dedicated to applications of next generation sequencing to unraveling genetic and molecular bases of rare diseases.

Submission deadline for proposals: March 24, 2016, 5:00 pm

Rationale

Deciphering the genetic and molecular bases of rare diseases is far from being achieved and remains of paramount importance to elucidate the pathogenic mechanisms of the diseases and for the development of diagnostic approaches and of innovative therapeutics.

The recent development of massively parallel DNA sequencing technologies has provided a new and potentially powerful way to identify almost all the mutations responsible for Mendelian disorders. Whole exome sequencing (WES) studies have allowed the identification of a growing number of genes responsible for rare monogenic diseases and the number of discovered genes increases significantly day after day.

Whole genome sequencing (WGS) may ultimately become the preferred technique for all gene discovery projects, as it aims to uniformly and completely cover exomes as well as non-coding regulatory, deep intronic and intergenic sequences. WGS is also probably a strategy of choice when detection of complex structural variants represents an important element of investigation.

However, given the current state of the technology, the high cost still associated, the important resources needed for analysis and the challenge of interpreting genomic variants, the expected benefits of conducting a WGS project still must be carefully considered and balanced with the chances of success using WES before applying for WGS projects.

Most research have focused so far on germline highly penetrant monogenic causes of diseases but new research directions now emerge. Genotype-phenotype correlation studies, as illustrated for instance in intellectual disabilities, indicate that phenotype are only rarely explained completely by a mutation in a single gene. The quest to identify and reliably interpret non-coding, somatic and complex genetic causes of diseases is just beginning.

Several approaches combining different techniques could be proposed, for instance:
- WGS with RNA-seq and adapted bioinformatic tools which may allow identification of non-coding variants with evidence of altered gene expression, and help to decode mechanims and pathways by which non coding RNA regulates gene expression,
- deep sequencing and comparative studies, which could highlight hypotheses of constitutive and somatic mosaic mutations,

- miRNA expression deregulation and epigenetic changes, which can now be assessed in the etiology of diseases or in association with the phenotypic variability of diseases.

These new findings are driven by constant and rapid cutting-edge technological advancements that are now offering the possibility to address scientific issues, even at the single-cell scale, and are creating new opportunities for biomarker, preventive or therapeutic approaches.

Program description

The goal of the open call for proposals is to support hypotheses driven research projects aimed at exploring genetic and molecular bases of rare diseases by the use of next generation sequencing approaches (Exome, Genome, RNA-seq, small RNA-seq, ChIP-seq, Methyl-seq, …) to make progress in the understanding of rare diseases with the aim to improve therapeutic strategies.

Priority will be given to projects that focus on well-characterised clinical phenotypes for which a genetic basis is postulated, that show potential leading to molecular diagnosis or therapeutic approaches in clinics, and for which applicants can demonstrate the availability of expert bioinformatics hub.

Successful applicants will have a facilitated access to the latest improvements and most appropriate techniques developed by experienced sequencing academic platforms and private companies, partners of the French Foundation for rare diseases.
Information about sequencing platforms/companies partners are available on the website (professional access; http://fondation-maladiesrares.org/appels-a-projets). If specific needs are required by applicants for their projects, please contact the Foundation at ngs@fondation-maladiesrares.com in order to evaluate conditions of services.

This program is open to research projects covering all rare diseases.
For rare cancers, the French National Cancer Institute, INCa, and the French Foundation for rare diseases have defined jointly the following criteria:
- high throughput sequencing projects concerning primary malignant tumors should be addressed to INCa,
- projects concerning benign tumors as well as systemic rare diseases involving tumor development will be evaluated within this call.

The aim of the call is in compliance with the goals set by the International Rare Diseases Research Consortium (IRDiRC).

Instructions and Guidelines

Proposal submission and schedule of the call

To complete and submit an application form, please access to the portal **"Applicant portal".**

Submission deadline for proposals: **March 24, 2016 (5:00 pm)**.

Proposals will be sent for evaluation to external referees and selected by a scientific *ad hoc* committee, composed of members of the Scientific Advisory Board of the French Foundation for rare diseases and NGS experts. The selection results will be communicated by e-mail to the principal investigator in July 2016.

Eligibility criteria

- The principal investigator of the project must belong to a French research team**,** affiliated to academia (research team working in universities, other higher education institutions or research institutes) and/or to clinical/public health sector (research team working in hospitals/public health organizations).
- This program is intended for analysis of **qualified existing samples only** and will not support participant enrollment, consent or biosample collection for new studies. Consents for analysis of DNA samples for research purpose must be obtained prior to apply to this program.

Requirements for full proposals

- *Applicants resubmitting projects are required to provide a detailed answer to the comments provided by the Scientific Committee of Fondation maladies rares at the previous session and highlight changes in the revised version.*
- *Applicants, who were principal investigators or partners in a project or whose team was previously funded by the GIS-Institute for rare diseases or by Fondation maladies rares since 2009 are required to provide a detailed report on the results and impacts of all ended projects. For ongoing projects, a detailed progress and / or preliminary data report is required.*

  Report forms are available on the applicant portal and on the website of the French Foundation for rare diseases fondation-maladiesrares.org or upon request by using: ngs@fondation-maladiesrares.com

  Please attach all reports to the proposal.

If these items are not fully answered, the submitted project will not be considered for funding.

Funding

Fondation maladies rares provides financial support for next generation sequencing and bio-informatics analyses provided by the sequencing platforms/companies acting as partners of the foundation. Funding cannot include equipment or personal costs. Possible co-funding of projects must be specified.

DNA samples

DNA samples (quality checked) MUST be available at time of project submission and will be sent at time specified by the Foundation after reception of the approval letter.
Project funding will be lost if samples cannot be sent in a timely manner.

Shared database of rare variations

Applicants submitting projects agree that the genomic data obtained through funding from Fondation maladies rares will be released after anonymization into a national shared database of rare variations, that will be linked to the RD-Connect platform, a project funded by the European Commission as a contribution to the IRDiRC goals and guidelines.

Communication

The title of the selected projects and name of their principal investigator will be published on the website of Fondation maladies rares (http://fondation-maladiesrares.org).

Acknowledgement Policy: It is required that projects funded by the French Foundation for rare diseases be acknowledged in all publications and communications. Reference(s) of the publication(s) must be sent to the foundation.

IRDiRC policies and guidelines: the project partners are expected to follow IRDiRC policies and guidelines. For more information see http://www.irdirc.org