

## Call 2021, October: 'GenOmics of rare diseases'

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

***Submission deadline for proposals: December 2, 2021, 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 researches 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 phenotypes 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 mechanisms 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, etc.) 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.

Projects based on exome sequencing of modifying genes are henceforth considered outside the scope of the call.

Successful applicants will have a facilitated access to the latest improvements and most appropriate techniques developed by experienced sequencing academic platforms and private companies.

Information about sequencing platforms/companies partners of the French Foundation for rare diseases are available on the website (<https://fondation-maladiesrares.org/les-plateformes/>). If specific needs are not covered by partner platforms, please contact the Foundation at [aap-bio@fondation-maladiesrares.com](mailto:aap-bio@fondation-maladiesrares.com) in order to evaluate conditions of services.

For projects not using conventional WES nor conventional WGS, technical issues must have been discussed with platforms before submission to ensure feasibility of the project. Applicant will provide a detailed budget (based on a quote provided by a platform) of the sequencing and data analysis.

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: **December 2, 2020 (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 by March 2022.

### 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). **Early career scientists are encouraged to apply as principal investigator.**

\* This program is intended for analysis of **qualified existing biosamples only** and will not support participant enrollment, consent or biosample collection for new studies. Consents for analysis of 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 the French Foundation for Rare Diseases 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 French Foundation for Rare Diseases since 2017 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 or upon request by using: [aap-bio@fondation-maladiesrares.com](mailto:aap-bio@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**

The French Foundation for Rare Diseases provides financial support for next generation sequencing and bio-informatics analyses provided by the sequencing platforms/companies acting as partners of the foundation. Please clearly indicate the part(s) of your project for which you request financial support. Funding will cover costs of services provided by the platform and is not intended to cover equipment, running costs or personnel costs in the researcher's laboratory. Possible co-funding of projects must be specified.

### **Samples**

For WES and WGS projects, samples (quality checked) MUST be available at time of proposal submission and will be sent at time specified by the Foundation.

Project funding will be lost if samples cannot be sent in a timely manner.

For other NGS approaches, the principal investigator must justify he/she has the necessary budget for samples preparation and detail it in the proposal.

### **Shared database of rare variations**

Applicants submitting projects agree that the genomic data obtained through funding from the French Foundation for Rare Diseases 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 the French Foundation for Rare Diseases (<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>