PhD position:
“ Deciphering the Variant of unknown Significance of RYR1 gene: Classif AI RYR1 ”

SECTOR: Higher Education Institution

LOCATION: Grenoble, FRANCE

INSTITUTION: CNRS

RESEARCH FIELD:
Molecular Modeling / Computational biology & statistics (ML)/ Molecular genetic

SCIENTIFIC DEPARTMENT:
*Unité Médicale de Génétique Moléculaire (CHU Grenoble Alpes);
*Laboratoire TIMC (CNRS UMR 5525);
*Département de Pharmacochimie Moléculaire (CNRS UMR 5063)

DOCTORAL SCHOOL: Doctoral School of Chemistry and Life Sciences
SUPERVISOR’S NAME: Dr Julien Fauré
PROJECT COORDINATOR’S NAME: Dr John Rendu (molecular geneticist)
OTHER CLOSE COLLABORATORS:
   *Dr Aline Thomas (molecular modeling),
   *Dr Antoine Frenoy (computational biology)

TYPE OF CONTRACT: doctoral contract
CONTRACT LENGTH AND STARTING DATE: 3 years (36 months) starting on September / October 2021
JOB STATUS: Full time (35 hours per week)
WAGE: monthly raw salary ~ 2135€ (standard CNRS salary for PhD students) equivalent to about 1700€ net

SUBJECT DESCRIPTION OR MISSIONS

The genetic screening of patients affected by rare diseases results in the identification of responsible gene(s) for about 50% of the patients. The remaining 50% are in a diagnostic deadlock for two major reasons: i) the genes involved in the disease are not yet identified, ii) we are not able to determine if the variant(s) found in a gene is (are) pathogenic or benign. The complexity of some genes make this classification particularly difficult.

In neuromuscular rare diseases, RYR1 is one of the most frequently mutated gene. It is involved in a complex clinical continuum ranging from a susceptibility trait for peranesthesia malignant hyperthermia to foetal akinesia. Among this continuum, various myopathies have been identified and classified according to their mode of inheritance (recessive, dominant disorders) and the anatomical defaults observed on a muscle biopsy. This continuum is referred to as RYR1 related myopathies (RRM)
The coding sequence of the *RYR1* gene spans over 15,000 nucleotides and encodes a protein of 5,038 amino acids. To date, more than 2,850 variants have been identified in its sequence. Although the *RYR1* gene and protein have been studied for more than 20 years, their size and complexity obstruct the diagnosis. The majority of missense variants identified in *RYR1* are classified as "Variant of Unknown Significance" (VUS) and cannot lead to a conclusive diagnosis: a potential mutation has been identified, but it is not known if it is responsible for the pathology. The classification of these variants therefore remains a major challenge, as it is currently only validated by functional studies. However, these functional studies are generally long and complex, and therefore cannot be performed for the 1,216 VUS identified in *RYR1*. A reliable classification of these missense variants is urgently needed to resolve the diagnostic deadlock linked to this gene.

**The objective of the project is to create an efficient classification pipeline for *RYR1* variants of unknown significance.**

Through the gathering of experts in different fields (genetics, protein modeling, artificial intelligence, cell biology, and clinicians of Filnemus rare disease network), we propose to create this pipeline. Based on data from the literature and from the French network of neuromuscular diseases, this project will make use of homology modeling softwares and of available experimental 3D structures of RyR1 to derive structural and physico-chemical hints about the impact of genetic variations. This data will be used to train machine learning algorithms to predict the effect of new variants. The classification pipeline will be complemented with functional analyses at the cellular and animal levels (drosophila or mouse), and should result in the classification of 60 to 80% of the *RYR1*-VUS. Once finalized, the model will be available to the community for the diagnosis of rare diseases. If successful such methods could be further extended to other complex genes/proteins.

The PhD student will integrate a translational network of experts and will be the cornerstone of the project. The overall aim is to identify key elements able to mark the pathogenicity of known *RYR1* variants so that a reliable predictive tool can be generated.

The first step of the project will be to build reliable 3D models of human RYR1 from the experimentally determined structures (by electron microscopy and crystallography) and closely related RYR1 structures (from rabbit until now). This step involves homology modeling, loop modeling, energy minimizations. The second step will be to derive appropriate structural and physico-chemical descriptors from the achieved 3D model of human RYR1. The data generated will be integrated in a database. The third step will be to train, test and validate an AI Model to classify the variant of unknown significance. This AI model will be corrected by the functional validation that will be realized by the teams working in Myoneuralp consortium that collaborate to this project. These laboratories have developed several *in vitro* studies and/or animal models to reproduce *RYR1* mutations.
ELIGIBILITY CRITERIA AND EXPECTED PROFILE

Applicants must hold a Master's degree (or be about to earn one) or have a university degree equivalent to a European Master's (5-year duration)

**Desired skills:**
Programming, Structural biology, Genetics, Data analysis and statistics

Given the strongly interdisciplinary nature of the project, some of these skills can be acquired or strengthened during the PhD. Overall, two different profiles could be accepted:
1/ Relevant practice in Molecular Structural analysis with a willing to develop computational experience (especially machine learning, and integrative data analysis pipelines)
2/ Relevant practice in programming, statistics and machine learning and a strong interest in protein 3D modeling.

**For both profiles:**
*Very good communication skills and an interest for interdisciplinary work: the candidate will have important interactions with geneticists, computer scientists and structural biologists.*
*Academic background on rare diseases or genetics would be appreciated but is not mandatory.*

**Desired professional experience:**
Research experience in one of the involved fields, ideally 2 periods of at least 3 months in a laboratory

APPLICATION PROCESS

Applicants will send their application **as a single PDF file** containing
- A CV,
- An application letter in English,
- Their last diploma and/or transcript,
- The names and contact details of references (recommendation letters may also be sent directly to john.rendu@univ-grenoble-alpes.fr).

Application review will begin on 7th July 2021 and last until the position is filled

The selected candidates will be invited for interviews in Grenoble or via zoom by mid August 2021

Address to send applications: john.rendu@univ-grenoble-alpes.fr
Potential applicants should feel free to reach Dr. Rendu for informal enquiries.