2018 Helmholtz – OCPC – Program
for the involvement of postdocs in bilateral collaboration projects

PART A

Title of the project: Multi-Omic diagnostics of Mitochondrial diseases

Helmholtz Centre and institute: HMGU, Institut of Human Genetics

Project leader: Dr. Holger Prokisch

Web-address: https://www.helmholtz-muenchen.de/ihg/research/groups/research-group-genetics-of-mitochondrial-disorders/overview/index.html

Description of the project (max. 1 page)**:**

The care of rare Mendelian diseases has been revolutionized by genome sequencing. While in the past it could be a long, frustrating and often losing battle for parents with an affected child to find the cause of their child's suffering, the availability of genome sequencing has made this - at least conceptually - possible for every patient. Knowing the causal mutation can be key for treatment, removes uncertainty that can be torturing and distracting, and may inform future family planning. However, this promise has not been fully delivered. Across a large variety of Mendelian diseases, analysis of the coding sequence does not lead to diagnosis for 50-75% of patients. This figure indicates that in numerous cases the pathogenic variant evaded detection, was detected but remained as a variant of uncertain significance (VUS), or involved a more complicated interaction. Such VUS can be coding as well as non-coding variants affecting RNA abundance or isoform. Metabolic disorders in which the pathology is present and measurable/accessible on the cellular level are particularly amenable to study and validate the molecular disease mechanism.
To improve existing diagnostic tools and patient care, we focus on mitochondrial diseases given the breadth of their genetic basis and the possibility for rapid functional validation of candidate pathogenic variants in patient cell lines. Mitochondrial diseases are the most frequent inborn errors of metabolism, collectively affecting 1 in 5,000 individuals. They represent a vast and highly heterogeneous group of more than 300 rare diseases, therefore representing a *pars pro toto* for Mendelian diseases. Our approach require multi-omics data, which, by tracking the effect of mutation along the pathway of RNA abundance, to protein levels, and cellular and tissue phenotypes, narrows down the search space and can drastically improve the success rate of genetic diagnosis. We require algorithms to integrate multi-omics data and generate testable hypotheses on candidate genes and variants. We need rapid cycles between patient visits, hypothesis generation, experimental validation, and translation into patient care. Such an endeavor in the setting of rare diseases requires a critical mass that can only be achieved by international collaboration.

Clinical management of mitochondrial diseases is mainly focused on symptom management. The heterogeneity presents a major challenge in designing a general treatment strategy. During recent years, more than 40 cofactor metabolism defects have been discovered, resulting in impaired mitochondrial energy metabolism amendable to supplementation of the affected factor, thus highlighting the importance of diagnosis of such conditions. These discoveries – and more are expected – have already led to personalized rational treatment of more than 100 diagnosed patients in our centers.
In the project we will i) create a collection of >500 fibroblast cell lines with a clinical relevant biochemical defect; ii) expand the diagnostic tools to RNA-seq and quantitative proteomics; iii) develop and apply a diagnostic multi-omics pipeline; iv) validate novel disease genes, variants and mechanisms, and v) translate diagnosis into patient care. This project will create the critical mass needed to develop new tools to boost Mendelian diagnostics and serve as a catalyst for translating basic research results into clinical practice.

Description of existing or sought Chinese collaboration partner institute (max. half page)**:**
With this application, we wish to bring together groups with unique expertise for the biochemical and genetic diagnosis and care of patients with mitochondriopathies and computational scientists who have developed multi-omics database and statistical models for diagnostics.

An already existing collaborator is, Prof. Fang Fang, Head of Neurology department, National Center for Children's Health, Capital Medical University, Beijing Children's Hospital (BCH), NO 56 Nanlishi Road, Xicheng District, Beijing 100045.

The National Center for Children's Health, Capital Medical University, Beijing Children's Hospital, is the largest children's hospital and medical center in China, and directs key national laboratories. It has focused on mitochondrial disease for over 20 years, and represents the Chinese mitochondrial disease research center.

Applications by postdocs of this and other organizations with a strong background in mitochondrial medicine, rare disorder research or multi-omics integration are invited to apply.

Required qualification of the post-doc:

The multidisciplinary approach followed requires and integrates expertise from different areas, clinical, bioinformatic and cellbiology. The applicant could come from any of the three areas.

- PhD in i) bioinformatics or ii) biology or iii) MD with specialisation in neurology or genetics
- Experience in one of the three areas i) integrating and analysing genomic, transcriptomic and proteomic data, or ii) investigation of mitochondrial (dys-) function, cell biology, enzymatic and molecular biological studies, or iii) clinical characterisation, diagnosis and treatment of patients with mitochondrial disorders
- Additional skills in one of the other areas

PART B

Documents to be provided by the post-doc, necessary for an application to OCPC via a postdoc-station:

- Detailed description of the interest in joining the project (motivation letter)
- Curriculum vitae, copies of degrees
- List of publications
- 2 letters of recommendation
- Proof of command of English language

PART C

Additional requirements to be fulfilled by the post-doc:

- Max. age of 35 years
- PhD degree not older than 5 years
- Very good command of the English language
- Strong ability to work independently and in a team