Neurodegenerative diseases (NDs) are very polymorphic and affect people of all ages. They concern both rare diseases and more common diseases. Improving knowledge of NDs in the French Caribbean region requires special attention because of the unique environmental and genetic background of its populations. In Martinique, there is a huge need for scientific research on rare NDs. While epidemiological and clinical research has increased over the past decade in the French West Indies, there is still little or no data on the genetics of NDs in these regions. The advent of Next Generation Sequencing (NGS) on a global scale has the potential to make a difference in this field, provided that technological and analytical knowledge, based on bioinformatics, is available in Martinique. Caribbean Reference Center for rare neuromuscular and neurological disorders (CERCA), is a reference center for diagnosis, health care and treatment of rare NDs. It supports our capacity building project in the clinical characterization of rare NDs with motor impairment, with or without dementia. In collaboration with CERCA, we designed a two-step pilot study, consisting of: 1) the creation of a clinical and biological database to select informative cases, and 2) to screen them by whole exome sequencing. This innovative approach involves: 1) mobilization of medical and clinical knowledge for the characterization of rare ND, with the support of a register of experts, and 2) expertise in molecular biology, molecular pathways and bioinformatics. This preliminary study confirms the need to consider our French West Indian population in these specificities. It reveals the effectiveness of a well-tune database for identifying pathogenic variants in a cohort of French West Indian patients with presumed genetic NDs, associated with motor impairment with or without dementia. It is a proof of concept that the creation of a register of NDs and the mastery of NGS technique, can provide additional expertise in research and patient management in the Caribbean. The continuation of this capacity building project should increase CERCA's skills and outreach. Such an initiative is clearly innovative for the region and would bring the Caribbean, Latin America and North America communities together, around the subject.

INTERNATIONAL AND NATIONAL CONTEXT AND ISSUES

As neurodegeneration is one of society's "major challenges", research on neurodegenerative diseases (NDs) has been a European priority for more than 10 years. The organization called "Join Project Neurodegenerative Diseases Research" has ruled on the necessity to organize European research on neurodegenerative diseases, and to develop a partnership with Latin America and the Caribbean countries, where populations have different environmental and genetic backgrounds that could be a model study.¹

The first French health plan for neurodegenerative diseases was drafted in 2014 for a period of five years. The directions and actions of the Neurodegenerative Diseases Plan (in French, "PNMD") are part of the National Health Strategy and the National Research Strategy. It has 5 main priorities:

- Improve patient diagnosis and management.
- Ensure the quality of life of patients and their caregivers.
- Develop and coordinate research.

The plan for the period of 2014-2019 concerns all patients with Alzheimer's disease, Parkinson's disease and multiple sclerosis, and is extends to all neurodegenerative diseases. The plan includes other disabling neuropathic diseases, such as Huntington's disease, motor neuron diseases (such as amyotrophic lateral sclerosis), spinocerebellar...
ataxies or prion diseases. Their prevalences are low but they often include a family component. Neurodegenerative diseases are very polymorphic and affect all ages of life. They concern both rare diseases and more common diseases. The French government has been publishing health plans to fight rare diseases in particular, since 2005. For the clinical diagnosis and management of rare diseases, the French government encourages the creation of reference centers.

In the French West Indies (FWI), the Caribbean reference center for rare diseases has been specialized in the diagnosis of neuromuscular and neurological disorders since 2006. It is called the "Caribbean Reference Center" (CERCA) and is located at the "Centre Hospitalier Universitaire" (CHUM), in Fort-de-France, Martinique. CERCA coordinates medical consultations in Guadeloupe and French Guiana. Consultations are held regularly in the islands of Saint Lucia and Dominica. CERCA also receives patients from other Caribbean areas, according to their requests. The FWIs are particular French territories: Martinique and Guadeloupe are Caribbean islands, and French Guiana is located on the Latin American continent. The French Caribbean countries were inhabited by Caribbean Amerindians and were later populated mainly by African and European migrations, as well as Indian. The inhabitants of these French-speaking countries are therefore atypical French from an environmental and genetic point of view, but typical West Indians resulting from a unique genetic mix, just like other independent Caribbean peoples.

LOCAL AND REGIONAL CONTEXT AND ISSUES

Since 2015, Martinique has been a member of the Organization of Eastern Caribbean States (OECs). It is an international intergovernmental organization dedicated to economic harmonization and integration, to the protection of human and legal rights, and the promotion of good governance between independent and non-independent countries in the Eastern Caribbean. Our island is therefore involved in the development of centers of excellence in public health for the OECs, in the achievement of economies of scale, the dissemination of knowledge and experience, and in the research synergy to improve the quality of care and health care delivery. Strengthening the capacity of CERCA, which is already involved in the diagnosis and treatment of Caribbean patients with ND, would reinforce its excellence and its outreach, while helping to improve the skills of neighbouring islands.

Capacity building through the creation of a registry is the first argument of our approach. It is a process of individual and institutional development that leads to higher levels of competence and a greater capacity to conduct useful research. Population-based registries provide public health surveillance and research. Health indicators generated by population registers are useful, not only for the population, but also for:

- health facilities and local authorities
- public health decision-makers
- clinicians and researchers.

To develop sustainable epidemiological surveillance and evaluation, as well as effective research programs on rare ND in the Caribbean, the entry of clinical and molecular data into a registry will be crucial: the production of reliable epidemiological data, improving management, reduction of mortality and so on.

Considering the Caribbean population origins, genetic determinism must be explored, in order to explain certain specificities of Caribbean NDs. Some local specificities remain clinically determined and published, such as atypical Parkinsonism in Guadeloupe/Martinique, but there is no local or specific epidemiological database on NDs, whereas the epidemiological register of cancers and fetal malformations in the FWI has already existed for more than 20 years for the first and 10 years for the second. As the literature on genetics of NDs in the Caribbean is rather poor, collaborations consisting of a transfer of know-how and experience from these highly qualified registers to a NDs register will be considered, both at the local and Caribbean level.

AN INNOVATIVE PROJECT IN EVERY RESPECT THAT OPENS UP NEW PERSPECTIVES

The main objective of this study is to highlight causal mutations in targeted rare diseases, presumed genetic, for which the classical molecular diagnostic pathway has not been able to identify a causal mutation. There are many secondary objectives:

- describe the clinical characteristics of the targeted pathologies in Martinique
- describe the modes of transmission of family pathologies
- provide diagnostic assistance
- allow genetic counselling
- test a new experimental device
- highlight local specificities
- initiate the establishment of a register of clinical data specific to targeted diseases in Martinique.

The first step of our capacity building project is to develop a clinical and biological database on NDs associated with motor disability, with or without dementia, in Martinique. It is a cornerstone and a stepping stone for our pilot study. The second step of our capacity building project consists in highlighting the potential of the register in the selection of cases on which to carry out the molecular research program. More than 80% of rare diseases are genetically determined, but many rare diseases remain unexplained at the molecular level. With the advent of next-generation sequencing (NGS), the world of molecular diagnostics and genetic investigation strategies is changing on 2 main levels:

1. We are moving from a genetic medicine based mainly on monogy to a genetic medicine open to polygenism.
2. Clinical limitations can be overcome by interrogating gene panels.

THE NGS, A TOOL OF CHOICE FOR OUR INVESTIGATIONS

Gene panels are currently used for the diagnosis of NDs according to their expression and whole exome sequencing is used for the molecular diagnosis of NDs with a motor im-
Capacity building in clinical and molecular characterization of rare neurodegenerative diseases through the development of...
The preliminary results of our study are encouraging in terms of resolving cases without identified mutations and highlighting the described rare mutations. This capacity building project is a proof of concept because it allowed us to:

- identify very rare mutations in dominant and recessive SCA families
- exclude digenism in the family case of ALS with anticipation
- propose candidate genes in the case of AMS.

It is also proof of our ability to solve clinically, diagnostically and molecularly important problems ourselves, especially at much lower costs than existing networks.

**DISCUSSION**

**THE PROJECT CONFIRMS THE NEED TO CONSIDER OUR WEST INDIAN POPULATION IN ITS SPECIFICITIES**

The capacity building project is based on an innovative process. This process combines the construction of a database, and the deployment of a new NGS data analysis capability. On the one hand, the database should form the basis for a register of rare NDs, which implies the mobilization of medical and clinical knowledge for the characterization of rare neurodegenerative diseases. On the other hand, increasing the capacity to analyse and interpret NGS data will improve skills in molecular biology, molecular pathways and bioinformatics.

The project objective is to clarify local specificities in terms of surveillance and research on rare NDs with motor impairment with or without dementia. The 1st step consists in accurately collecting clinical, biological and genetic data; the 2nd step consists in developing local capacities in innovative technologies such as NGS. Through this project, we were able to identify:

- a particular local phenotype in Huntington’s disease
- a phenomenon rarely described in amyotrophic lateral sclerosis
- mutations that could not have been identified from the routine diagnostic process.
- particular mutations.

This pilot study demonstrates the effectiveness of the process in improving the clinical and molecular characterization of rare ND diseases and promoting research in this area. It confirms the need to consider our West Indian population in its specificities. We demonstrate the incredible potential for research and clinical surveillance of rare diseases associated with motor impairment with or without dementia, developed from the establishment of a local register, and the improvement of our expertise in genomic analysis and bioinformatics.

The search for a genomic mutation is becoming less expensive and less constraining. Bioinformatics plays a central role in this development. Henceforth, the deployment of a genomics service dedicated to the search for genetic mutations in Martinique should be achievable to take advantage of the benefits of clinical and fundamental research in the Caribbean population, particularly in the NDs.

**LIMITATIONS OF THE STUDY**

The only limit of this project remains the funding. It is essential to sustain our capacities and implement our project whose objectives are crucial and are already enshrined in national and European health policies.

**CONCLUSIONS**

**THE PROJECT OPENS UP OPPORTUNITIES FOR COLLABORATION**

The collaborations set up should make it possible to perpetuate our project and develop research partnerships on the subject in the Caribbean. Such a dynamic will enable...
our center to become one of the centers of excellence in research and surveillance of rare diseases, a vector of attractiveness for medical and scientific cooperation.

Beyond the essential project of strengthening the characterization capacities of West Indian patients suffering from NDs in Martinique, the challenges of this project also concern:

- the sharing of experiences and data
- access to technological innovation
- in fine, the avenues of therapeutic research.

This project opens up the possibility of many related works. In this instance, we were able to develop the NGS, but we could imagine other biological study schemes (such as metabolomics, epigenetics, and so on). This project is an opportunity to bring health professionals together around an electronic collection of biological and medical data. This allows us to consider scientific studies on a larger scale, in the inter-region. As with all challenges that affect multiple communities, a collaborative project with the University of Antilles and others, should be required to improve the characterization of local specificities and diversities in rare NDs.

In France, scientists and medical communities are trying to regulate access to genome-wide technologies in order to offer the same level of diagnostic quality throughout the country. Given our geographical location and our various local needs, it would be interesting to develop our expertise in genomics and bioinformatics.

THE PROJECT PROMOTES COOPERATION

Due to the geographical and ethnic proximity of the Caribbean populations, the needs for scientific research on rare NDs associated with motor impairment with or without dementia, are similar throughout the region. This project should make it possible to initiate collaborations with existing or emerging research programmes in the Caribbean. It meets the expectations of the "Join Project Neurodegenerative Diseases Research", in terms of investigations of the Latin American and Caribbean populations.

As a general rule, Martinique’ health professionals are trained in medical cooperation for the exchange and identification of needs for additional health training. This is an important issue in our outermost regions, which are involved in the Organization of Eastern Caribbean States (OECs).

In the field of rare ND diseases, collaborative efforts will map and model health data for this sector within the Caribbean region. These efforts should also help to highlight the importance of structuring the sometimes complex management of patients with rare NDs, with or without dementia.

CERCA is already a Caribbean reference centre, but this clinical and molecular capacity building project is an additional means of expertise. It strengthens medical research prospects and contributes to the emergence of innovative clinical, diagnostic or therapeutic tools in terms of patient service.

Our project was entirely financed by private funds raised by the Caribbean Society of Myology. We now need more local collaborative partners to bring research capacity in the Caribbean region to its optimal potential for the diagnosis and treatment of rare ND associated with motor impairment with or without dementia. While the Caribbean is only now trying to build its capacity in genetic testing, Trinidad and Tobago has already been doing so since 2015, as have our other parents from sub-Saharan Africa.

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