Identification of new causative genes in spinocerebellar degenerations by combination of whole genome scan, next-generation sequencing and biological validation in vitro and in vivo

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Identification of new causative genes in spinocerebellar degenerations by combination of whole genome scan, next-generation sequencing and biological validation in vitro and in vivo

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Research Abstract

Spinocerebellar degenerations, which comprise cerebellar ataxias and hereditary spastic paraplegias (HSP), are neurological disorders characterized by progressive movement difficulties variably associating other neurological signs. They are genetically heterogeneous with >100 loci and >50 genes known to be implicated. They, however, account for only 40% of the patients. Our first objective is thus to identify new causative genes, which is crucial for diagnosis, for a better follow-up of patients and for a better understanding of the physiopathology by the identification of critical causative pathways. Currently, there is no available cure for these disabling diseases. Positional cloning using large informative pedigrees for disease gene mapping followed by candidate gene sequencing was until recently a state-of-the-art method to identify the causative mutations. However, the majority of patients belong to small families that are often under the threshold of informativity for linkage analyses. We thus propose to combine genome linkage mapping with next generation sequencing followed by a validation pipeline comprising bioinformatics and biological validations of the variants in basic models to facilitate the identification of causative variants in small families. To this end, we will take advantage of the world-largest cohort of patients with these disorders centralized by Teams 1 and 4 that comprise altogether >10,000 patients ascertained with identical clinical criteria. Among these families, Partners 1 and 4 have selected a series of 82 informative kindreds; 28 of them have already been explored by genome linkage analysis. This analysis has mapped candidate regions co-segregating with the disease. These regions are rarely shared among families indicating high genetic heterogeneity in this cohort and therefore high probability of multiple gene identifications during the course of this project. We intend to take advantage of the preliminary genome scan analyses to identify the causative mutations in these families by targeted capture and sequencing. The analysis of the sequencing data will be done using a bioinformatics pipeline (Partner 2) followed by functional validation of the most promising variants in vitro (Partner 1, cell models) and in vivo by modeling and rescue experiments in zebrafish embryos (Partner 3) and, when tools are available, in C. elegans (Partner 4). Finally, determination of the frequency and spectrum of the mutations and associated phenotypes of newly identified causative genes will be possible in the unique series of patients available, an invaluable knowledge for genetic counseling of these very disabling and often lethal disorders. Our second objective should pave the way to the study of the functional pathways and finally result in a better comprehension of the mechanisms underlying these disorders by opening new avenues of research and treatments for potentially up to 60,000 patients in Europe. First the genetic approach will enable to build a comprehensive network involving all known genes in these pathologies (Partner 2), which may help designing common therapeutic avenues. We are also particularly interested in 2 genes frequently mutated in HSP: SPG11 and SPG15. We will explore their dynamics of interaction in vitro (Partner 1) and in vivo using C. elegans (Partner 4). A systematic RNAi screen to identify modifiers of the phenotype will provide lists of potential candidate genes in HSP, which will reinforce the bioinformatics pipeline of the genetic approach for this project.
This project will be a pilot study in Europe for large-scale elucidation of the molecular bases of neurodegenerative diseases using a genetic and functional validation pipeline. All teams involved in this project are complementary and a Portuguese PhD student (funded by FCT (Portugal) co-directed by Partners 1 (France) and 4 (Portugal) will ensure part of its feasibility.

Further information available at:

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