## Abstract

Clinical variants of dementia are limiting their diagnosis and can leads to underdiagnosing or substitution of two different diseases with the same symptomatology. The aim of this study is a better understanding of a factors involved in the clinical variability of rare dementias. Progressive supranuclear palsy and Gerstmann-Sträussler-Scheinker syndrome caused by mismatch mutation P102L in Prion protein are used as model diseases. In this thesis, we firstly demonstrate the influence of the distribution of neuropathology and its spread on the clinical phenotype of the disease. Although a single neurodegenerative disease increases the risk of neurodegenerative comorbidity, this other neuropathology does not affect the phenotypic presentation of the primary disease. Monogenetically inherited proteinopathies can have a different clinical subtype, which is not only conditioned by causal protein polymorphisms, but can be influenced by the wild type allele of causal protein. A more accurate understanding of the symptomatic variability in dementias will allow a better focus of a drug studies and, in the future a treatment, but it will also lead to a better understanding of the pathogenesis of neurodegenerative diseases.

**Keywords:** dementia, Progressive supranuclear palsy, Gerstmann-Sträussler-Scheinker syndrome, variability, phenotype, neuropathology