

Understanding the role of interruptions in polyQ diseases
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Scientific Abstract

At least eight dominant spinocerebellar ataxias (SCAs) are caused by an expansion of polyglutamine (polyQ) tracts in the corresponding gene products, which leads to polyQ mediated protein misfolding and aggregation and eventually to neuronal cell death. Each disease is associated to a specific threshold, that is around 35-40 glutamines, above which the pathology occurs. It has however been observed that silent or non-silent interruptions may strongly modulate the effect of expansion on pathology.

The present proposal aims at understanding which and how the nature and the length of interruptions alter the properties of polyQ and which and how many residues in polyQ tracts are necessary to influence pathology. We hope the results of this study will clarify the diagnosis in those cases where the expanded allele falls in the intermediate range. This will be valuable in a clinical setting and for genetic counselling. The work is intended as an integrated interdisciplinary effort between UCL, where sequencing of normal and expanded SCA alleles directly from ataxia patients will be carried out to determine underlying sequence variations not detected by sizing alone, and NIMR where structural studies will be performed to understand how the same variations influence the aggregation properties and the toxicity of the polyQ containing proteins. It is expected that the output of this work will provide direct help in diagnosis/counselling and eventually lead to potential future therapy.

Lay Summary

At least eight inherited spinocerebellar ataxias share similar genetic causes and molecular mechanisms. They are all caused by mutations in the respective gene, which consist of irregular expansions in tracts corresponding to the production of specific proteins. The expansions confer abnormal properties to the mutant protein, which becomes insoluble and prone to form toxic deposits inside the affected neurons. In a small number of cases however, it has been observed that the severity of the abnormalities may be strongly modulated by the presence of interrupting signals in the expanded tract, although the precise effect or the mechanism by which they work is still unknown.

We plan to start a new line of research which addresses for the first time how the length and the nature of the interruptions affect spinocerebellar ataxia pathology. We plan to study examples in which patients carry interrupted expansions, and try to rationalise these results by laboratory studies which will tell us how the nature and length of the interruptions influence the properties of the mutant proteins. This information will be essential for patients and subjects at risk and of crucial importance



in diagnosis and counselling, particularly with respect to prediction of age at onset and progression of the disease as well as to the probability of further genetic expansion when transmitted to future generations.

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