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Polyglutamine Disorders

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Preface

On Polyglutamine Diseases

Polyglutamine (polyQ) diseases are a group of rare neurodegenerative disorders that share a common genetic cause: they arise as a result of abnormal expansions of CAG trinucleotide sequences occurring at particular genome loci. In contrast with other repeat-related disorders, the repeat-bearing tracts associated with polyQ diseases are present at the codifying region of genes, being translated as expanded polyQ tracts in their respective protein products. Although these genes and proteins are otherwise unrelated and share no significant homology outside the CAG/polyQ tract, proteins carrying an abnormally expanded polyQ tract tend to aggregate, forming insoluble protein aggregates that constitute a key neuropathological feature of polyQ disorders. The group currently includes nine disorders: Huntington's disease (HD), dentatorubral-pallidoluysian atrophy (DRPLA), spinal and bulbar muscular atrophy (SBMA), and six different types of spinocerebellar ataxia: SCA 1, 2, 3, 6, 7, and 17. PolyQ diseases are highly incapacitating and, to this date, no therapy able to modify disease progression is available for any of them.

PolyQ disorders share several features. These include (a) the existence of a positive correlation between the variable CAG repeat number and both the severity and precocity of symptoms; (b) the generational instability in CAG repeat number transmission; and (c) the aforementioned propensity for the protein products to aggregate and to constitute large intracellular multiprotein inclusions that are detected in patients' neuronal tissue. Despite the genetic cause of polyQ disorders being clearly identified, the molecular mechanisms involved in their pathogenesis are not fully understood. Though it is frequently accepted that these disorders share common pathogenic mechanisms, the symptoms and the regional patterns of neurodegeneration are not shared among disorders. Taken together, the similarities and differences existing in this group of disorders suggest that the search for disease mechanisms and putative therapeutic strategies will benefit from an integrative view that conjugates common factors and motifs with the particularities of each polyQ disease.

For this book entitled *Polyglutamine Disorders*, we have gathered many of the main experts around the world in the field, whom we would like to acknowledge for their work and collaboration, providing a state-of-the-art revision about several aspects of the different polyQ diseases. The book addresses the molecular mechanisms described to underlie disease pathogenesis, the animal models developed to study these diseases and, importantly, the advanced therapeutic strategies being investigated for these disorders.

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