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Polyglutamine ataxias: From Clinical and Molecular Features to Current Therapeutic Strategies

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Abstract

Spinocerebellar ataxias are a large group of heterogeneous diseases that all involve selective neuronal degeneration and accompanied cerebellar ataxia. These diseases can be further broken down into discrete groups according to their underlying molecular genetic cause. The most common are the polyglutamine ataxias, of which there are six; Spinocerebellar ataxia type 1, 2, 3, 6, 7 and 17. These diseases are characterised by a pathological expanded cytosine–adenine–guanine (CAG) repeat sequence, in the protein coding region of a given gene. Common clinical features include lack of coordination and gait ataxia, speech and swallowing difficulties, as well as impaired hand and motor functions.

The polyglutamine spinocerebellar ataxias are typically late onset diseases that are progressive in nature and often lead to premature death, for which there is currently no known cure or effective treatment strategy. Although caused by the same molecular mechanism, the causative gene and associated protein differ for each disease. The exact mechanism by which disease pathogenesis is caused remains elusive.

However, the variable (CAG)n repeats are codons that may be translated to an expanded glutamine tract, leading to conformational changes in the protein, giving it a toxic gain of function. Several pathogenic pathways have been implicated in polyglutamine spinocerebellar ataxia diseases, such as the hallmark feature of neuronal nuclear inclusions, protein misfolding and aggregation, as well as transcriptional dysregulation. These pathways are attractive avenues for potential therapeutic interventions, as the potential to treat more than one disease exists. Research is ongoing, and several promising therapies are currently underway in an attempt to provide relief for this devastating class of diseases..

The spinocerebellar ataxias (SCAs) are a large group of typically late onset, progressive disorders characterised by neurodegeneration and other pathologically heterogeneous clinical features .These diseases are often grouped into categories based on their causative mutation, of which there are three: 1. Non-coding repeat ataxias, where the repeat expansion is located outside the protein coding region for the gene of interest. 2.

Ataxias where disease is caused by an ‘orthodox’ mutation, such as missense or splice site mutation. 3. Polyglutamine (polyQ) ataxias where the disease is characterized by an expanded cytosine–adenine–guanine (CAG) repeat located in the coding region of the respective gene.As the triplet CAG encodes for the amino acid glutamine, this leads to an elongated glutamine tract in the translated protein resulting in conformational changes that are thought to cause several pathogenic mechanisms.

Although the presence of an expansion does not necessarily correlate to phenotypic modifications, once a threshold for a specific gene is met, this tends to lead to disease and pathogenesis. Due to the nature of these mutations, the pathogenic severity and penetrance is typically determined by the size of the expansion, where there is a common trend: the larger the expansion, the more severe the pathogenesis and/ or the earlier the onset [4]. These diseases tend to follow what is known as ‘genetic anticipation’, whereby the expansion size increases with each successive generation [5,6]. It should be noted that the genetic anticipation in most SCA diseases is typically more likely to be passed down from the paternal gene rather than the maternal. Rare cases have been reported where individuals possess two

mutant alleles, leading to more severe symptoms than individuals with just one mutant allele.

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