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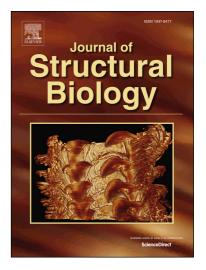
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Polyglutamine expansion diseases: More than simple repeats

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## ACCEPTED MANUSCRIPT

#### Polyglutamine expansion diseases: More than simple repeats

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#### Abstract

Polyglutamine (polyQ) repeat-containing proteins are widespread in the human proteome but only nine of them are associated with highly incapacitating neurodegenerative disorders. The genetic expansion of the polyQ tract in disease-related proteins triggers а series of events resulting in neurodegeneration. The polyQ tract plays the leading role in the aggregation mechanism, but other elements modulate the aggregation propensity in the context of the full-length proteins, as implied by variations in the length of the polyQ tract required to trigger the onset of a given polyQ disease. Intrinsic features such as the presence of aggregation-prone regions (APRs) outside the polyQ segments and polyQ-flanking sequences, which synergistically participate in the aggregation process, are emerging for several disease-related proteins. The inherent polymorphic structure of polyQ stretches places the polyQ proteins in a central position in protein-protein interaction networks, where interacting partners may additionally shield APRs or reshape the aggregation course. Expansion of the polyQ tract perturbs the cellular homeostasis and contributes to neuronal failure by modulating protein-protein interactions and enhancing toxic oligomerization. Post-translational modifications further regulate self-assembly either by directly altering the intrinsic aggregation propensity of polyQ proteins, by modulating their interaction with different macromolecules or by modifying their withdrawal by the cell quality control machinery. Here we review the recent Download English Version:

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