It's the size that counts

Influence of Huntingtin peptide length on its conformational ensemble and binding to DNAJB1

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In Short

- Formation of β-amyloid fibers by the peptide HTTExon1 causes Huntington's disease.
- The number of glutamine residues in the sequence and thereby the size of HTTExon1 defines the onset of the disease.
- Chaperones like DNAJB1 can suppress the formation of these neurodegenerative fibers.
- The structure of HTTExon1 (varying lengths) and its influence on DNAJB1 binding are unknown.
- Enhanced computational simulation protocols are used to unravel the peptide's structure and assess the difference in protein-peptide complex formation.

Huntington's disease (HD) is a hereditary neurodegenerative disorder, which is caused by the peptide huntingtin (HTT). HTT is a large ubiquitous protein of 3144 amino acids and involved in numerous physiological processes and its large interaction network also suggests a general scaffolding role [1]. In the event of post-translational modifications, HTT is processed to become a smaller peptide (HTTExon1), consisting of an important region, containing only glutamine (Q) amino acids. The expansion and size of this polyglutamine stretch defines about the onset of the disease. The disease pathology is fully penetrant above the threshold of Q>39 (Figure 2). Above this threshold, HTTExon1 is responsible for the formation of the pathology's hallmark amyloid structures found in both the cytoplasm and nucleus of HD patient's neurons. Below the threshold HTTExon1 resides in its soluble form. A recently identified multi chaperone complex [2] can however prevent the formation of neurodegenerative β-amyloid fibers. HD causes atrophy of the basal ganglia, a result of the extensive loss specifically of medium spiny neurons of the striatum [3] (Figure 1).

This project aims at the structure predictions of the key player peptide Huntigton in the context of the Huntington disease. No experimental structures of the whole HTTExon1 peptide are available, independent of the size of the peptide. Detailed understanding of the binding processes of HTTExon1 are however necessary to understand the mechanism behind the prevention of fiber formation.

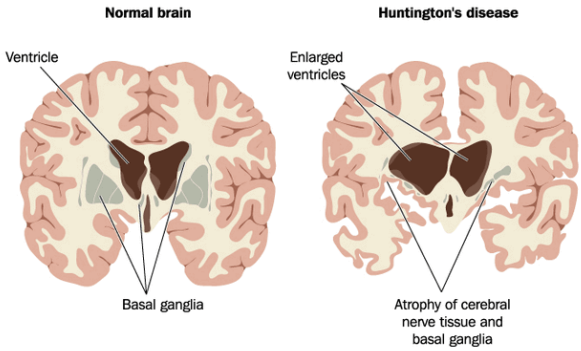

***Figure 1:** Scheme showing brain sections of a normal brain and one affected by the Huntington's disease. HD affected brain shows enlarged vesicles, due to the atrophy of basal ganglia. Figure accessed through: https://www.medanta.org/patient-education-blog/huntingtons-disease—a-rare-genetic-disorder-of-the-brain/*

Peptide structures can be perfectly accessible via molecular dynamics simulation but require a confidential ensemble of structures, especially for disordered peptide, exhibiting a high conformational flexibility. Therefore, classical homology model approaches would not generate reliable three dimensional peptide structures, but rather only serve as input for more advanced sampling protocols. In this project we aim for the structure prediction of HTTExon1 via the enhanced sampling technique TIGER2h [4], sampling the peptide's phase space by heating of all atoms over a replica ladder and frequent exchanges between configurations. Thereby, a folding and unfolding of HTTExon1 is simulated, in which energetically different minimum structures are possible to be explored. The presented algorithm requires the simulation of more than 20 simulation cells simultaneously, for which parallel computing is a necessity.

Once suitable peptide structures with varying poly-Q length have been generated, the binding of HTTExon1 variants to the chaperone DNAJB1 is performed. Mainly the question "What are key interactions that enable HTTExon1 with poly-Q>39 to bind to DNAJB1? is expected to be answered. The overall aim of this study is the elucidation of structural details regarding the mechanism behind HTTExon1 aggregation and the prevention by chaperones like DNAJB1, in order to provide valuable knowledge for disease treatment.

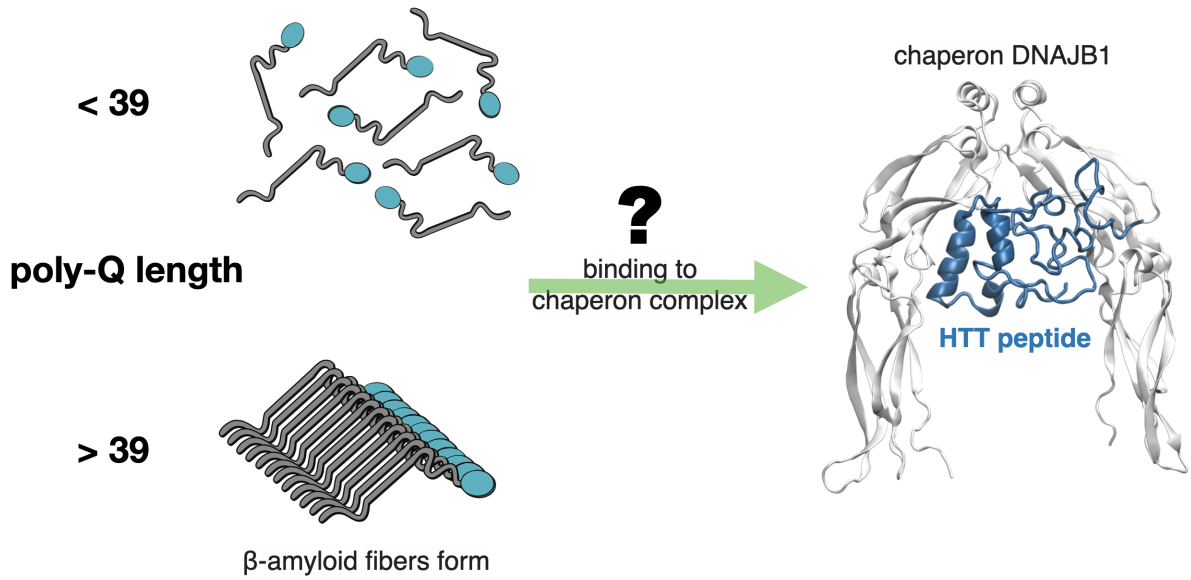

Figure 2: *Scheme showing the impact of the poly-Q length of HTTExon1 on its aggregation behaviour and binding to the chaperone DNAJB1.*

WWW

https://www.hmi.uni-bremen.de/Koeppen/koeppen_home.html

More Information

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[2] Scior A, Buntru A, Arnsburg K, Ast A, Iburg M, Juenemann K, Pigazzini ML, Mlody B, Puchkov D, Priller J, Wanker EE, Prigione A, Kirstein J. *EMBO J* **2**, 282-299 (2018). doi: 10.15252/embj.201797212

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[4] Kulke M, Geist N, Möller D, Langel W. *J Phys Chem B* **29**, 7295-7307 (2018). doi: 10.1021/acs.jpcb.8b05178

Project Partners

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