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Length and sequence dependence in the association of Huntingtin protein with lipid membranes SUDI JAWAHERY, ANU NAGARAJAN, SILVINA MATYSIAK, University of Maryland, College Park — There is a fundamental gap in our understanding of how aggregates of mutant Huntingtin protein (htt) with overextended polyglutamine (polyQ) sequences gain the toxic properties that cause Huntington's disease (HD). Experimental studies have shown that the most important step associated with toxicity is the binding of mutant htt aggregates to lipid membranes. Studies have also shown that flanking amino acid sequences around the polyQ sequence directly affect interactions with the lipid bilayer, and that polyQ sequences of greater than 35 glutamine repeats in htt are a characteristic of HD. The key steps that determine how flanking sequences and polyQ length affect the structure of lipid bilayers remain unknown. In this study, we use atomistic molecular dynamics simulations to study the interactions between lipid membranes of varying compositions and polyQ peptides of varying lengths and flanking sequences. We find that overextended polyQ interactions do cause deformation in model membranes, and that the flanking sequences do play a role in intensifying this deformation by altering the shape of the affected regions.

Sudi Jawahery
University of Maryland, College Park

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