Title:	An intrinsically disordered pathological prion variant Y145Stop converts into self-seeding amyloids via liquid–liquid phase separation
Authors:	Agarwal, Aishwarya (/jspui/browse?type=author&value=Agarwal%2C+Aishwarya) K. Rai, Sandeep (/jspui/browse?type=author&value=K.+Rai%2C+Sandeep) Avni, Anamika (/jspui/browse?type=author&value=Avni%2C+Anamika) Mukhopadhyay, Samrat (/jspui/browse?type=author&value=Mukhopadhyay%2C+Samrat)
Keywords:	An intrinsically disordered pathological prion variant Y145Stop amyloids
Issue Date:	2021
Publisher:	PNAS
Citation:	Proceedings of the National Academy of Sciences of the United States of America, 118(45).
Abstract:	Biomolecular condensation via liquid–liquid phase separation of intrinsically disordered proteins/regions (IDPs/IDRs) along with other biomolecules is proposed to control critical cellular functions, whereas aberrant phase transitions are associated with a range of neurodegenerative diseases. Here, we show that a disease-associated stop codon mutation of the prion protein (PrP) at tyrosine 145 (Y145Stop), resulting in a truncated, highly disordered, N-terminal IDR, spontaneously phase-separates into dynamic liquid-like droplets. Phase separation of this highly positively charged N-terminal segment is promoted by the electrostatic screening and a multitude of weak, transient, multivalent, intermolecular interactions. Single-droplet Raman measurements, in conjunction with an array of bioinformatic, spectroscopic, microscopic, and mutagenesis studies, revealed a highly mobile internal organization within the liquid-like condensates. The phase behavior of Y145Stop is modulated by RNA. Lower RNA:protein ratios promote condensation at a low micromolar protein concentration under physiological conditions. At higher concentrations of RNA, phase separation is abolished. Upon aging, these highly dynamic liquid-like droplets gradually transform into ordered, β-rich, amyloid-like aggregates. These aggregates formed via phase transitions display an autocatalytic self-templating characteristic involving the recruitment and binding-induced conformational conversion of monomeric Y145Stop into amyloid fibrils. In contrast to this intrinsically disordered truncated variant, the wild-type full-length PrP exhibits a much lower propensity for both condensation and maturation into amyloids, hinting at a possible protective role of the C-terminal domain. Such an interplay of molecular factors in modulating the protein phase behavior might have much broader implications in cell physiology and disease.
Description:	Only IISER Mohali authors are available in the record.
URI:	https://doi.org/10.1073/pnas.2100968118 (https://doi.org/10.1073/pnas.2100968118) http://hdl.handle.net/123456789/4396 (http://hdl.handle.net/123456789/4396)
Appears in Collections:	Research Articles (/jspui/handle/123456789/9)

File	Description	Size	Format	
Need To Add…Full Text_PDF..pdf (/jspui/bitstream/123456789/4396/1/Need%20To%20Add%e2%80%a6Full%20Text_PDF..pdf)	Only IISER Mohali authors are available in the record.	15.36 kB	Adobe PDF	View/Open (/jspu

Show full item record (/jspui/handle/123456789/4396?mode=full)

(/jspui/handle/123456789/4396/statistics)