Researchers uncover physics involved in a key process in Huntington's disease

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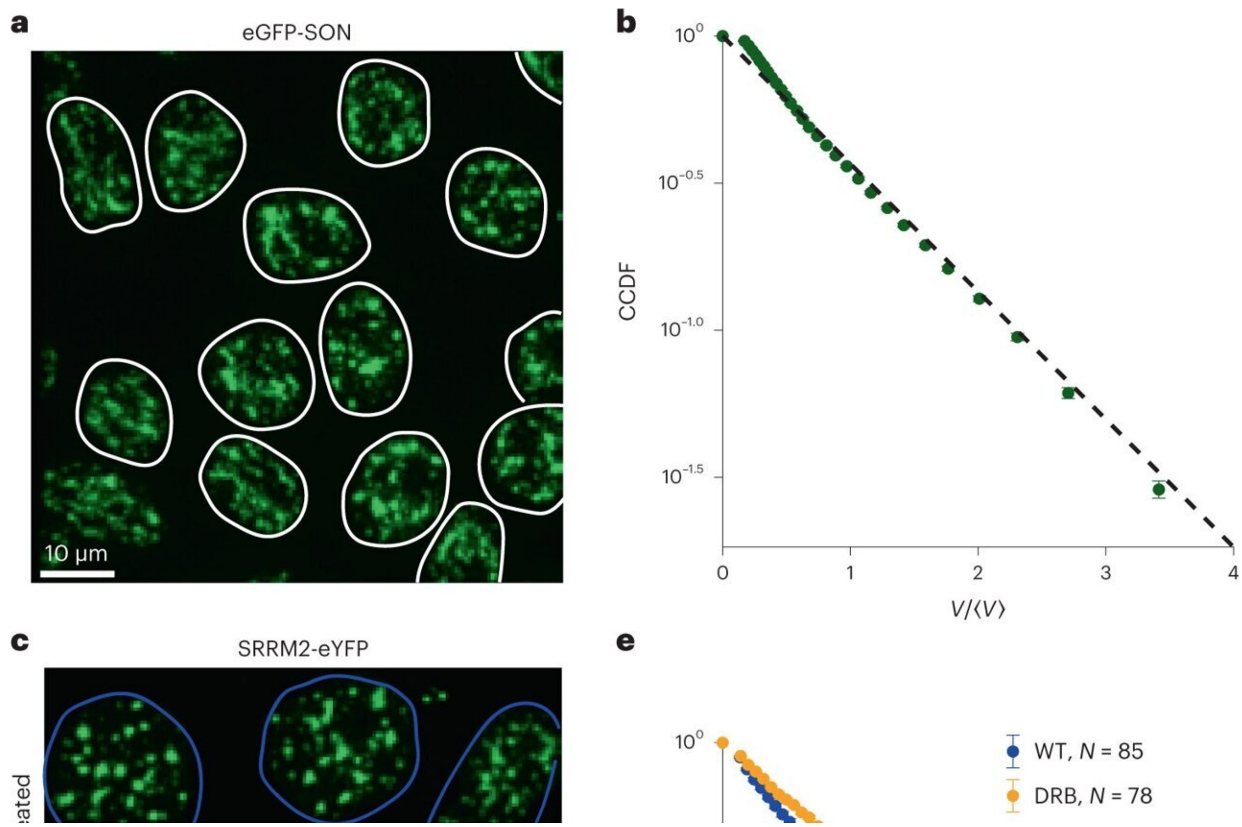

Endogenous nuclear speckles display exponential distributions before and after transcriptional inhibition. a, Exemplary maximum-projected image of iPSCs tagged with eGFP-SON and imaged in three dimensions. Nuclear outlines are highlighted in white. b, For each nucleus (N = 453), speckles were segmented in three dimensions, and the CCDF was calculated, rescaled by mean speckle volume in each nucleus and averaged over the nuclei, revealing good agreement with an exponential distribution (dashed line). The error bars reflect the standard error of the mean (s.e.m.) over the cells. c, Nuclear speckles were labelled in

HEK-D cells by tagging SRRM2 with eYFP and imaged in three dimensions; nuclear outlines are highlighted in blue. d, Treatment with the transcriptional inhibitor DRB resulted in larger, brighter speckles and aberrant nuclear morphology. Nuclear outlines are highlighted in orange. e, CCDF was calculated for both non-treated control (N = 85; blue points) and following 4 h of treatment with 50 μg ml–1 DRB (N = 78; orange points), resulting in an increase in average speckle size from 0.92 ± 0.02 to 1.16 ± 0.03 μm3 (mean ± s.e.m.), giving linear CCDFs with slightly different slopes on a semi-log plot. Collapsing by rescaling by the average speckle volume (inset) confirms that both distributions remain exponential. The error bars reflect the s.e.m. over cells. Credit: *Nature Physics* (2023). DOI: 10.1038/s41567-022-01917-0

Researchers from Princeton University have uncovered the physics of a cellular process linked to aggregation diseases, including Huntington's disease, paving the way to a deeper understanding of neurodegenerative disorders at the molecular level.

Many critical systems within a cell function inside liquid droplets that are separated from their surrounding fluids the way oil gathers in water. Scientists have only recently realized the importance of these droplets, especially in the kinds of processes that lead to cell breakdown and death.

The Princeton-led team found that as such droplets drift in their surrounding liquid, they collide and gather into larger droplets in mathematically predictable ways. The math that describes this aggregation is similar to how internet memes go viral or scientific papers accumulate large numbers of citations. Abnormally large droplets in brain cells are linked closely to ALS, Alzheimer's and a range of other dysfunctions.

The work was led by Princeton faculty members Ned Wingreen, the

Howard A. Prior Professor in the Life Sciences, and Cliff Brangwynne, the June K. Wu '92 Professor in Engineering. Brangwynne described the work as "important for establishing a quantitative framework for understanding the fundamental physical mechanism behind protein aggregation, a necessary step for developing treatments for these devastating diseases."

The paper is published in the journal *Nature Physics*.

More information: Daniel S. W. Lee et al, Size distributions of intracellular condensates reflect competition between coalescence and nucleation, *Nature Physics* (2023). DOI: 10.1038/s41567-022-01917-0

Provided by Princeton University

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