Effects of Natural Selection on the Phase-Separation Properties of an RNA-Binding Protein in Mammals

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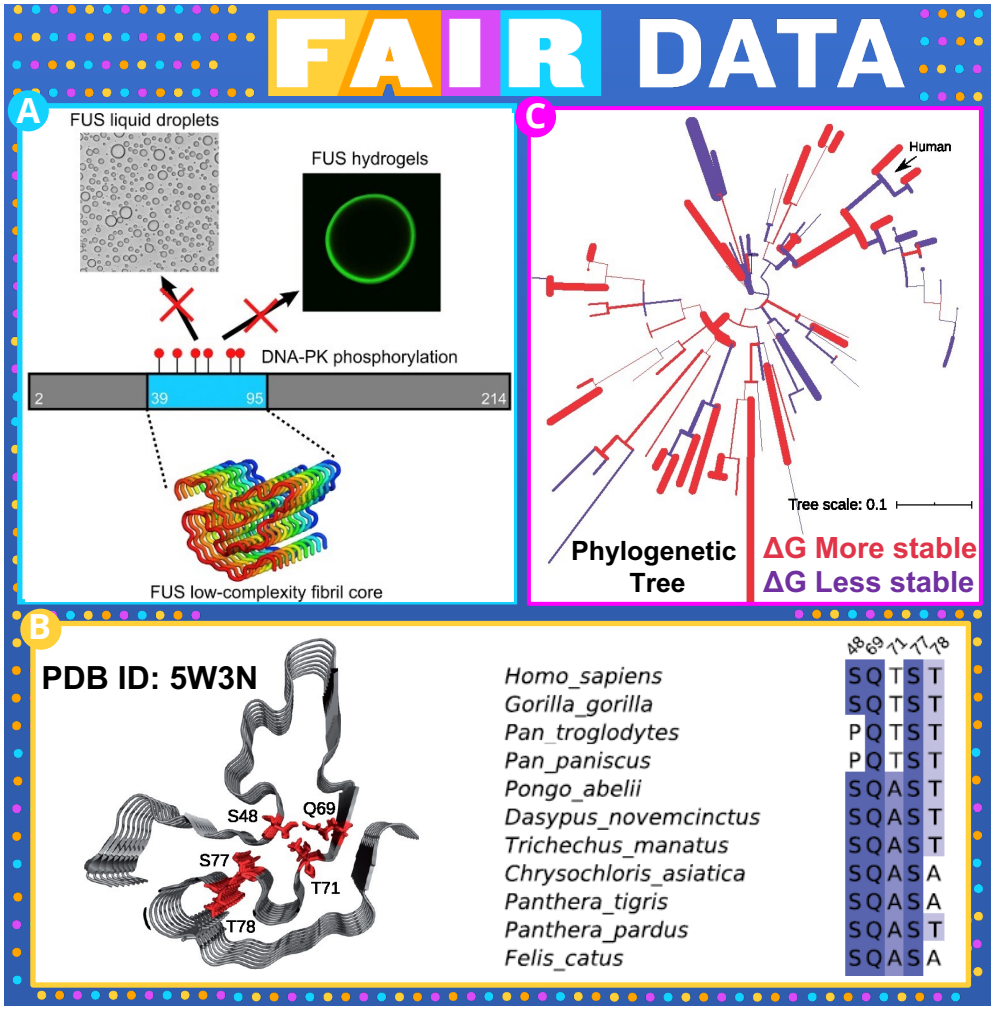
NMR users studying three-dimensional structures of large biological molecules, such as proteins and nucleic acids, frequently deposit data in the **Protein Data Bank** to ensure that it is **Findable**, **Accessible**, **Interoperable**, and **Reusable**.

Data users from Harvard and the University of Zurich accessed solid-state NMR data previously collected from the MagLab's 900MHz ultrawide bore NMR magnet that describes the molecular structure of self-assembling fibrils formed by the RNA-binding protein, "FUS". Mutations in FUS are associated with ALS disease pathology involving its ability reversibly form phase-separated liquid compartments at sites DNA damage. The NMR experiments revealed that formation of the liquid and hydrogel states of FUS is controlled by phosphorylation and stabilized by hydrogen bonding among a core region of 57 amino acids (**Figure A**).

The accessed data were used to examine the effects of naturally occurring amino acid substitutions that change the stability of the fibril core (**Figure B**) and predict differences in the Gibbs free energy of FUS folding among mammals (**Figure C**). *This new work provides evidence that natural selection has stabilized the liquid forming potential of FUS and minimized the propensity of cytotoxic liquid-to-gel phase transitions during 160 million years of mammalian evolution*.



Facilities and instrumentation used: NMR-MRI/S 900MHz 105 mm bore magnet
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Dataset: Protein Data Bank ID 5W3N