Protein phase separation is implicated in formation of membraneless organelles and membrane protein-associated puncta. It can be driven by multivalent pi interactions of intrinsically disordered protein regions, enabling us to develop a successful predictor of phase separation. Multivalent interactions between the disordered regulatory region of the CFTR chloride channel and calmodulin activate CFTR and may underlie membrane puncta formation associated with activation. Calmodulin binding mimics phosphorylation, enabling the nucleotide-binding domain dimerization that is required for activity and that is likely defective in cystic fibrosis-causing mutants, with instability of the second nucleotide-binding domain potentially playing a role in pathology.